Aisha Sie

Innovations in genetic testing and counseling: Patient experiences

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Innovations in genetic testing and counseling: Patient experiences

DOCTORAL THESIS

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by

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Chapter 1

General introduction

"Between the health care we have and the care we could have lies not just a gap, but a chasm."

(Institute of Medicine)

BACKGROUND

Genetics is a rapidly developing field of science. Just the last decade has seen its evolution from the first complete sequencing of a single reference human genome in 2003[1] to next generation sequencing nowadays allowing individual genome-wide analysis in clinical diagnostics.[2] Genetic counseling acts as its clinical counterpart, guiding both patients and families in the translation of their genetic information to day-to-day life.[3] Novel technological advancements and increased public awareness of genetic aspects of disease, as well as the growing call for more patient participation in medical decision-making[4] frequently lead to new models of genetic services.[5]

The focus of this thesis is the evaluation of patient experiences with innovations in genetic testing and counseling, mainly regarding hereditary cancer. The goal is to give further insight to both genetic and non-genetic health care professionals to provide appropriate support in the context of the new developments and to assess needs for further innovation regarding genetic counseling and clinical follow-up. This chapter first describes the standard cancer genetic diagnostic process[6] and how the evaluation of patient experiences has already helped shape this process. Next, the current theoretical models and literature regarding psychological effects of conventional genetic testing and counseling are summarized. Finally, research needs in each stage of the genetic diagnostic process are discussed within the context of two well-known hereditary cancer syndromes, followed by an overview of the thesis chapters.

Genetic Diagnostic Process

The standard process surrounding the diagnosis of hereditary cancer can be split into three stages:

1. **Recognition & Referral:** Patients at high risk for hereditary cancer are selected by non-genetic health care professionals (e.g. general practitioners, medical oncologists, surgeons, gynecologists) for referral to and further evaluation at a human genetics department.

2. **Genetic Testing & Counseling:** Clinical geneticists and genetic counselors provide in-depth counseling regarding the possibility and consequences of hereditary cancer. Patients may be offered genetic testing in this stage. The current standard generally includes two face-to-face genetic counseling sessions: pre- and post-test.[5]

3. **Follow-up & Prevention:** Should hereditary cancer be confirmed by genetic testing, these mutation carriers are recommended intensive surveillance or prophylactic measures for early cancer detection and prevention. Family relatives are also eligible for testing or surveillance.

Impact of patient experiences

Dissemination of health care innovations into clinical practice is a long standing challenge. Involved parties may be hesitant to adopt innovations when uncertain about the consequences[7] which may include the psychological impact on patients. Evaluating outcomes reported by patients themselves may reduce this uncertainty, therefore increase adoption of novel strategies experienced as beneficial.

Patient experiences have already influenced cancer genetic counseling, originally based on the genetic diagnostic process for Huntington's disease, a neurodegenerative disease without treatment options.[8] This Huntington protocol included two mandatory pre-test counseling sessions to ensure proper decision-making to start genetic testing, followed by a post-test session to discuss test results. Contrary to Huntington's disease, hereditary cancer syndromes are often actionable: prevention measures can be taken to effectively lower cancer mortality.[9,10] Therefore patients may feel empowered by this knowledge: they can take action i.e. control these high cancer risks.[11] Research confirmed that patients tested for hereditary cancer reported no long-term increase in psychological distress[12], leading to hereditary cancer clinics making the second pre-test session optional.[8]

However, considering increasing awareness therefore demand for cancer genetic testing, even this two visit model may hamper patient access to cancer genetic services. Alternative models must be developed and evaluated for their beneficial as well as adverse effects.[5]

Psychological Effects of Genetic Testing

Two main motivations were expressed by patients regarding their wish to start genetic testing: the need for information and the need for control[11]: once patients know that they are at an increased risk for developing cancer, they can take preventive measures.[9,10] But the possibility or presence of increased cancer risks may have a psychological impact in itself. This is demonstrated by a recent review[13] which identified six overarching themes as specific psychosocial issues of these patients:

1. *Coping with cancer risk*, such as reassessing their life and priorities after genetic counseling, but also positive thinking and changing lifestyle behavior;
2. *Practical issues*, including concerns about access to health or life insurance, negative effects on employment and the burden of waiting times in the genetic diagnostic process;
3. *Family-related problems*, mainly revolving around communication, from finding support to start genetic testing to disclosure of the test result to family members;
4. *Children-related problems*, such as worries that their children (mainly daughters) may be at an increased risk of cancer, as well as uncertainty how best to inform their children;
5. *Living with cancer*, fear and thoughts about the risk of developing cancer, side effects of preventive measures and the impact of cancer within their family;
6. *Emotions*, mainly in reaction to genetic test results, which can be both negative (distress, fear, anxiety) and positive (reassurance, relief, reduced anxiety).

These issues can be experienced by all individuals undergoing evaluation for hereditary cancer, allowing a normal range of psychosocial impact which is normally covered by standard genetic counseling.[8] However, about a quarter of patients experiences serious (i.e. clinically relevant) levels of psychological distress coming forth from these issues, which may require additional psychosocial support.[13] Therefore these six themes are also represented by the psychological outcomes used in many research studies to evaluate patient experiences of the genetic diagnostic process.[14]

Models of psychological distress

To understand psychological distress in the context of genetic testing for hereditary cancer, several conceptual models from health psychology can be used. Van Oostrom e.a.[15] previously applied Leventhal's Common Sense model of Self-regulation and Psychological Adjustment. This model used the individual's perception of illness as the basis for coping responses (monitoring i.e. actively seeking information about medical threats and blunting i.e. passively seeking distraction[16]) and psychological well-being. Pessimistic illness perception was related to high-risk perception (i.e. expectations),

causal attribution to genetic factors and passive coping, which in turn was related to hereditary cancer distress.[15]

An elaboration of the Common Sense model was proposed by Baum e.a.[17] This Stress and Coping model also included the test result, disease characteristics and social support as factors playing into the extent of psychological distress triggered by genetic testing. If the individual experiences the test result as dangerous (dependent on risk/illness perception and disease characteristics) or an excessive demand (dependent on coping style and social support), this leads to possibly serious stress.

The psychological studies described in this thesis are based on these conceptual models, evaluating characteristics such as coping style, risk perception and illness perception as possible influencing factors on the resulting level of psychological distress within the context of genetic testing.[14]

Psychological distress in hereditary cancer

Certain patients are at potential risk for serious psychological distress during genetic testing. A recent review of individuals tested for Lynch syndrome by Bleiker e.a.[18] showed that this included: female patients, index patients (i.e. the first person in a family to undergo genetic counseling/testing), patients with high cancer risk perception, high distress prior to counseling, a history of depression or professional psychological support, parental cancer during childhood or lack of social support. Most studies in this review focused on patients without a prior history of cancer (unaffected) who experienced clear psychological benefit (decreased cancer anxiety) if no mutation was identified, while those with mutations reported only short-term increases of distress without adverse long-term effects.[18] Similar results were found in patients tested for hereditary breast cancer.[12]

Another review by Landsbergen e.a.[19] focused specifically on patients already diagnosed with (colorectal) cancer: 25% of these already affected patients reported clinically relevant distress. This dropped to 13% after genetic counseling. After result disclosure, mutation carriers were more distressed than non-carriers, but their distress also returned to baseline levels over time.[19]

In summary, both affected and unaffected carriers may experience short-term psychological distress due to conventional genetic testing for hereditary cancer, but report no long-term effects. Innovations in cancer genetic testing and counseling discussed in this thesis are evaluated within this light, assessing whether patient experiences deviate from this known trend.

Stage I: Recognition & Referral

Colorectal cancer (CRC) and breast cancer (BC) are two of the most common types of cancer worldwide.[20] Both have well-known hereditary forms.[21] But due to the common occurrence of CRC and BC in the general population, it may be difficult to recognize these families at risk for hereditary cancer. However, hallmarks of most hereditary cancers are an early age of onset and a positive family history.[21] Syndrome specific clinical and family history criteria further help non-genetic clinicians determine the need for in-depth evaluation by a clinical genetic professional.

Colorectal cancer (CRC)

About 3% of CRC cases is estimated to be based on Lynch syndrome (LS) as the most common hereditary form of CRC.[22] LS is caused by a mutation in one of the mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6* and *PMS2*.[22,23] Unaffected LS carriers are at increased cumulative lifetime risk primarily for developing CRC (25-70%) and, in women, endometrial cancer (30-70%).[24] Age at diagnosis of LS-related CRC ranges from 41 to 54 years, significantly lower than sporadic CRC at an average age of 70 years.[25-28] While both sporadic and LS-related CRC arise from adenoma developing into carcinoma, this progression occurs more rapidly in LS patients.[29] Clinical suspicion of LS is based on several clinical criteria such as the revised Bethesda guidelines shown in Table 1.[30] CRC tumor material can be tested for molecular characteristics of LS, prior to DNA analysis for germline mutations.[29]

Table 1: Revised Bethesda guidelines for testing colorectal cancer (CRC) tumors for Lynch syndrome (LS).[30]

CRC < 50 years.
Presence of synchronous, metachronous colorectal or other LS-associated tumors*, regardless of age.
CRC <60 years with microsatellite instability-high histology (≥2 of 5 markers).
CRC in 1 or more first-degree relatives with a LS-associated tumor, with one of the cancers <50 years.
CRC in 2 or more first- or second-degree relatives with LS-related tumors, regardless of age.

* LS-associated tumors: malignancies of the endometrium, stomach, small intestine, bile ducts, ovaries, upper urinary tract and adenoma or carcinoma of the sebaceous glands.

Breast cancer (BC)

Less than 10% of BC cases are estimated to be based on a genetic predisposition, most commonly a mutation in the *BRCA1* or *BRCA2* genes leading to hereditary breast/ovarian cancer (HBOC).[21] Unaffected female *BRCA*-mutation carriers have a cumulative lifetime risk of BC up to 60-80% and an increased risk of ovarian cancer (OC) up to 20-60% for *BRCA1* and 2-20% for *BRCA2*[31-33] with a younger age of onset than sporadic tumors.[34] *BRCA*-mutation carriers affected with BC have an additional increased risk of a second primary

Table 2: Dutch national guideline "Breast cancer" (BC) criteria for referral to a clinical genetic professional due to increased BC risk.[36]

BRCA-mutation.
First degree relative with BC <40 years.
First degree relative with bilateral or multifocal BC, at least once diagnosed <50 years.
First degree male relative with BC, regardless of age.
BC <50 years and prostate cancer <60 years on one side of the family.
Two or more first degree relatives with BC <50 years.
Three or more first or second degree relatives with BC, at least once diagnosed <50 years.
First degree relative with ovarian or tubal cancer, regardless of age.

BC up to 60%.[35] Without preventive measures, the average survival until 70 years of age is 50% in *BRCA1* and 70% in *BRCA2*.[10] To identify patients at high risk for a *BRCA*-mutation, the Dutch national guideline "Breast cancer"[36] contains criteria to determine eligibility for referral to a clinical genetic professional as shown in Table 2.

Research needs: detection of hereditary cancers

Despite aforementioned criteria for referral to clinical genetics due to suspected hereditary CRC or BC, recent studies have shown that both LS and HBOC remain underdiagnosed.[37,38] Attempts to improve clinician knowledge and referral patterns[39] were not successful.[40] This demonstrates the need for innovative alternatives to improve recognition of LS and HBOC. Some improvement was achieved by direct CRC tumor genetic testing for LS based on the Bethesda guidelines, which previous studies showed was cost-effective[41,42] and did not lead to increased psychological distress in patients.[43] However, more improvements could be made to detect more families at hereditary risk for cancer, especially in HBOC where no such tumor genetic testing is available.

Stage II: Genetic Testing & Counseling

Once patients are referred for evaluation at a human genetics department, they are usually seen for genetic counseling to be advised about the most appropriate course of action (e.g. whether to start genetic testing). One of the core tenets of genetic counseling is non-directiveness: genetic counselors aim to guide patients to their own individual decisions, by helping them interpret their genetic information and weigh their different options in consideration of their personal situation.[44] During this process, aspects to consider may relate to the disease in question, the nature of the proposed genetic test, but also characteristics specific to individual patients themselves.[45]

Knowledge without action

Patients have reported a variety of motivations to start genetic testing for hereditary cancer.[11] On one hand, there are clear informational needs: wanting to understand their cancer risks, what actions can be taken, and how their family is affected. On the other hand, patients are also motivated by the need to feel a sense of control. This control could be represented by using their newfound knowledge of carrying a hereditary predisposition for cancer to take preventive actions and lower their cancer risks, effectively increasing their life expectancy.[9,10]

However, in hereditary adult-onset cancer syndromes such as LS and HBOC, cancer prevention measures are usually not offered until the age of 25 years, while patients can choose to start genetic testing from 18 years onwards.[45] This may leave a considerable time gap between these young adults' discovery of being a mutation carrier and the start of cancer surveillance. These young adult mutation carriers between 18 and 25 years may be particularly vulnerable to distress, being aware of higher cancer risks without the clear ability to act upon this knowledge until the age of 25[46] while still in the midst of developing into fully independent adults.[47,48]

Research needs: genetic testing in young adults

Specific support needs amongst young adults in familial adenomatous polyposis (FAP) have already been identified, partly resulting from the aforementioned discrepancy between testing and surveillance age.[49,50] However, FAP is associated with a much earlier onset of cancers in childhood with early prevention recommendations and therefore, by exception, allows genetic testing of minors. This complicates generalization to hereditary adult-onset cancer syndromes, where the legal adult age must be reached to undergo genetic testing.[45] Further study of this particular age group within hereditary adult-onset cancer syndromes may identify those patients in special need of support.

Next generation sequencing

Until recently, genetic diagnostic technologies could only investigate one individual gene per DNA sequencing test.[2] Therefore such conventional DNA-testing focused on single genes known to be associated with the disease in question, starting with the most likely candidate gene, such as the LS-related genes for CRC or the *BRCA1/2* genes for BC as the most common hereditary cancer syndromes.[51] However, some diseases show large genetic heterogeneity: for example, over 100 genes are associated with different forms of hereditary cancer.[52] Pinpointing most likely candidate genes for individual testing based on patient and family characteristics may be difficult due to overlap in cancer types, and sequential single gene testing is laborious, costly and time-consuming.[2]

Recent years have seen the advent of next generation sequencing (NGS). These novel NGS technologies allow for simultaneous testing of all genes at once, at increasingly higher speed and lower cost.[2] This may lead to a far more rapid genetic diagnosis, preventing patients from undergoing more invasive diagnostic procedures and providing early information about prognosis and family consequences. Genes not previously associated with or relating directly to the disease in question are also sequenced at the same time. There are two sides to this approach: while new disease-causing genes may be discovered, there is also the risk of finding mutations in genes leading to an unrelated disease (so-called unsolicited findings[53]) or variants of unclear clinical significance.[54] As of yet, the frequency and nature of such findings are unknown, but patients must consider this unique possibility of NGS, prior to giving informed consent.[53] This remains an important subject of discussion, even as NGS technologies are now steadily being implemented into clinical diagnostics.[55,56]

Research needs: psychological impact of NGS

Novel NGS techniques have several advantages over conventional sequential genetic testing, facilitating rapid identification of a genetic cause in highly heterogenic diseases. But there are also issues of concern, which have led to hesitancy amongst some genetic professionals to implement NGS technologies into clinical diagnostics. Concerns focus primarily on the ethical challenges for proper informed consent due to limited knowledge about the clinical impact of new disease-causing genes and unsolicited findings, and consequently the psychological impact on patients receiving such results.[51] Evaluation of early patient experiences with NGS in such a clinical diagnostic setting could elucidate whether psychological impact differs from conventional genetic testing and how to structure the informed consent and genetic counseling procedures to guide patients appropriately.

Stage III: Follow-up & Prevention

In hereditary cancer, knowledge is power: intensive cancer surveillance outside of population screening programs is usually recommended, allowing patients to effectively manage their high cancer risks. For example, LS patients are offered frequent CRC surveillance from age 25 years, consisting of biennial colonoscopy and removal of premalignant polyps.[57] This lowers CRC incidence and mortality with 60%.[58] Preventive surgery is generally not recommended, although in LS patients already diagnosed with CRC, the preferred surgery of choice is a subtotal (i.e. more extensive than standard partial) colectomy to lower the risk of a second CRC tumor.[59]

Hereditary Breast/Ovarian Cancer (HBOC)

Contrary to these straightforward CRC surveillance recommendations for LS, *BRCA*-mutation carriers are faced with more difficult prevention choices.[60] For early BC detection, female *BRCA*-mutation carriers are offered intensive BC surveillance[61] starting at age 25 years with yearly MRI and clinical breast examination, with additional yearly mammography from age 30 years. *BRCA*-mutation carriers may also opt for preventive mastectomy (PM) as survival benefits do not differ significantly[10], although PM does lower the risk of BC with associated treatments by 90%.[10] While most *BRCA*-mutation carriers who had undergone PM considered this as a positive experience and expressed relief by their lowered BC risk, this was not without cost. They also experienced unexpected bodily sensations following surgery (*feeling different*) and self-consciousness of the look of their new body (*looking different*), which negatively influenced their sexuality and body image.[62] However, surveillance also requires frequent time investment and patients facing the stress of these tests at regular intervals.[60] These costs and benefits must be weighed individually by each patient to make a well-informed choice befitting their personal situation.

Unlike BC surveillance, gynecological screening for the elevated OC risk is ineffective[63] as there are no known premalignant stages.[64] Thus *BRCA*-mutation carriers are recommended prophylactic bilateral salpingo-ophorectomy (pBSO) between the ages of 35-40 for *BRCA1* and 40-45 for *BRCA*2.[34,61] pBSO lowers the risk of OC by 80-85% and, if performed prior to menopause, the risk of BC with 50%.[10,65] Patients consider the decision to undergo pBSO as easier than the decision to undergo PM.[60] However, similar to PM, reducing OC risk by pBSO comes with a price. From a medical point of view, surgically-induced menopause increases the risks of cardiovascular disease and osteoporosis.[65] From a patient point of view, pBSO has negative effects on both physical and emotional levels.[62] Young women feel the additional burden and increased urgency of still wanting to achieve certain family life goals (e.g. childbearing wishes) before the future need for pBSO.[60,66]

Several patient specific characteristics have been associated with the choice for preventive surgery versus cancer surveillance such as age, personal history of BC, parity[67], high risk perception and a history of BC in a first-degree relative.[68] Possibly this decision-making process is also influenced by advice from their physicians.[69] Cancer prevention recommendations may differ between countries[70], medical specialties, and physicians with varying levels of experience with genetic testing.[71,72]

Research needs: follow-up of HBOC

BRCA-mutation carriers may be seen by a wide range of physicians in different levels of health care: first line of general practitioners, second line of regional hospitals and third line of university medical centers (UMC). Further research is needed to evaluate whether patients supported for cancer prevention in regional hospitals differ from those supported in UMCs, and how this might influence the decision-making process regarding cancer (especially BC) prevention. UMCs have expert teams specialized in hereditary cancer who may have a different focus in patient groups and advice, which might be most effective if matched to both patients' and regional specialists' needs.

Thesis Outline

This thesis contains the results of several studies mainly evaluating patient experiences in both current and novel procedures within the genetic diagnostic process. The sections of this thesis reflect the three stages of this process as described in this general introduction (**Chapter 1**). Individual chapters focus on a certain procedure within each stage; some evaluate current standard care to determine the need for further innovation, others assess the effects of novel procedures in practice.

The first part of this thesis addresses the stage **Recognition & Referral**, in which non-genetic health care professionals select high-risk patients to be referred to a human genetic department.

Chapter 2 describes efficacy and cost-effectiveness analyses of a recently proposed change in international guidelines for improved detection of Lynch syndrome, which would empower more patients and their family members to take preventive measures and lower their cancer mortality.

Chapter 3 outlines the study protocol to evaluate a novel procedure for patients with breast cancer, replacing initial face-to-face genetic counseling prior to DNA-testing (current practice) by telephone, written and digital information sent to patients' homes. Evaluation of this so-called DNA-direct procedure is described in **Chapter 4** (short-term follow-up) and **Chapter 5** (long-term follow-up).

The second part of this thesis refers to the stage **Genetic Testing & Counseling**, in which patients are seen by clinical geneticists or genetic counselors at a human genetics department.

Chapter 6 illustrates patient reported outcomes of testing for hereditary cancer before the recommended age of surveillance (25 years), to determine whether genetic testing between 18 and 25 years prior to the start of surveillance measures is acceptable to these young adult patients.

Chapter 7 contains results of the very first study evaluating early patient experiences of gene panels based on exome sequencing (one of the novel next generation sequencing technologies) in a clinical diagnostic setting, using quantified psychological measures.

The third part of this thesis pertains to the stage **Follow-up & Prevention**, in which patients with a hereditary predisposition for cancer are recommended intensive surveillance or preventive surgery.

Chapter 8 outlines the characteristics and experiences of female *BRCA*-mutation carriers with follow-up care in a regional or university hospital, evaluating the regional collaboration between second and third lines of health care for *BRCA*-mutation carriers.

Chapter 9 concludes this thesis with a general discussion on patient experiences with innovations in the genetic diagnostic process and future perspectives.

Chapter 10 summarizes this thesis as a whole, followed by a list of associated publications and acknowledgements of those individuals who have supported the work collected here in various ways.

STAGE I

Recognition and referral

"The world is full of obvious things which nobody by any chance ever observes."

(Arthur Conan Doyle)

Chapter 2

Fourfold increased detection of Lynch syndrome by raising age limit for tumour genetic testing from 50 to 70 years is cost-effective

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ABSTRACT

Background: Recognising colorectal cancer (CRC) patients with Lynch syndrome (LS) can increase life expectancy of these patients and their close relatives. To improve identification of this under-diagnosed disease, experts suggested raising the age limit for CRC tumour genetic testing from 50 to 70 years. The present study evaluates the efficacy and cost-effectiveness of this strategy.

Methods: Probabilistic efficacy and cost-effectiveness analyses were performed comparing tumour genetic testing of CRC diagnosed at age 70 or below (experimental strategy) versus CRC diagnosed at age 50 or below (current practice). The proportions of LS patients identified and cost-effectiveness including cascade screening of relatives, were calculated by decision analytic models based on real life data.

Results: Using the experimental strategy, 4 times more LS patients can be identified among CRC patients as compared to current practice. Both the costs to detect one LS patient (€ 9,437/carrier versus € 4,837/carrier), and the number needed to test for detecting one LS patient (42 versus 19) doubled. When family cascade screening was included, the experimental strategy was found to be highly cost-effective according to Dutch standards, resulting in an overall ratio of €2,703 per extra life year gained in additionally tested patients.

Conclusion: Testing all CRC tumours diagnosed at or below age 70 for LS is cost-effective. Implementation is important as relatives from the large number of LS patients that are missed by current practice, can benefit from life-saving surveillance.

Keywords

genetic – hereditary – colorectal cancer – Lynch syndrome – screening

Key Message

Recognising colorectal cancer (CRC) patients with Lynch syndrome (LS) can increase life expectancy for patients and relatives. By raising the age limit for CRC tumour genetic testing from 50 to 70 years, 4 times as many LS patients are detected, which is cost-effective when including family cascade screening. Implementation is important to reach relatives of LS patients missed by current practice.

INTRODUCTION

Identification of Lynch Syndrome (LS: confirmed germline mutation) amongst patients with colorectal cancer (CRC) leads to effective surveillance and can prevent premature deaths of these patients and their relatives.[58] LS is the most common hereditary form of CRC, accounting for 1-3% of all CRC.[24] Identification of LS is based on family history and young age at diagnosis of CRC (below age 50) as in the Amsterdam-II and Bethesda criteria (see online only supplemental S1[30,73]). Due to small families, unawareness of family history and current age limits, only a proportion of the expected number of LS patients is identified.[37] Unawareness of LS patients of their increased cancer risk and prevention options leads to unnecessary CRC incidence.

LS is caused by a mutation affecting one of the mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6* and *PMS2*.[22,23] LS patients have a high risk of developing CRC (25-70%), endometrial cancer (30-70%), and an increased risk for several other types of cancer (stomach, ovaries, urinary tract, brain, small bowel, hepatobiliary tract, skin).[24] Over 90% of LS-related CRC and 10-15% of sporadic CRC are characterised by microsatellite instability (MSI).[74] MSI-testing in newly diagnosed CRC patients fulfilling MIPA criteria (MSI Indicated by a PAthologist[42]: S1) based on Bethesda guidelines, including diagnosis below age 50, was shown to be cost-effective (€3,801/life year gained).[41]

Recently a European meeting of experts specialised in LS recommended an age limit of 70 instead of 50 years[24], thereafter incorporated in ESMO guidelines.[29] Updated NCCN guidelines advocate universal screening or selectively testing all CRC≤70 and CRC>70 fulfilling Bethesda criteria[75]; both strategies equally result in a higher diagnostic yield in comparison to the limit of 50 years.[76] However, no cost-effectiveness analyses were performed to justify the costs for additionally testing CRC patients diagnosed between ages 51-70 years.

Increasing the age limit from 50 to 70 years will greatly increase numbers to test: only 5-6% of CRC is diagnosed below age 50 versus 50% below age 70.[77] MSI-testing at higher age may be less effective as young age at diagnosis is a hallmark of hereditary cancer, and MSI-high tumours at older age more often are caused by non-hereditary *MLH1* promoter hypermethylation.[74]

To evaluate genetic testing of CRC diagnosed at age 70 or below (experimental strategy) versus age 50 or below (current practice) an economic evaluation was performed for newly diagnosed CRC index patients (i.e. first CRC patient tested within one family) including family cascade screening.

METHODS

Efficacy (proportion of LS patients identified amongst CRC index patients) was compared between the experimental strategy (CRC≤70) versus current practice (CRC≤50). Only age at diagnosis for one CRC tumour was considered, excluding criteria based on additional tumours or family history.[30,42] Cost-effectiveness analyses included both index patients and relatives tested by cascade screening. Effectiveness was expressed in life years gained and direct medical costs in Euros (€), based on the Dutch healthcare system, using a time horizon of average life expectancy.

Cost-effectiveness models

Three decision analytic models were developed using TreeAge version 2013. The first model (Figure 1) was aimed at efficacy, focusing on CRC index patients tested for MSI at age of diagnosis 70 or below (experimental strategy) versus 50 or below (current practice). The second model was aimed at cost-effectiveness (S2) using the same decision tree, but focusing on additionally tested index patients diagnosed with CRC between 51 and 70 years. Integrated Markov chain analyses (S3a) evaluated survival and follow-up

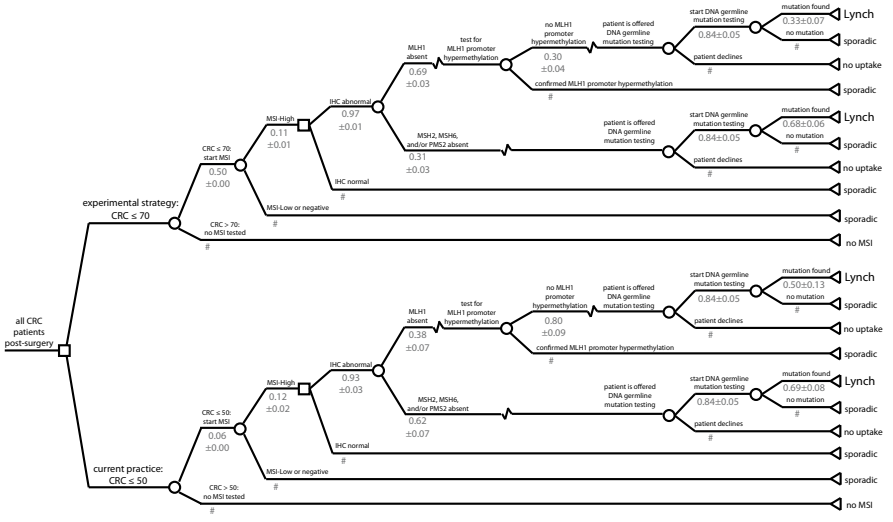

Figure 1: Patient-based decision analytic model for identifying Lynch syndrome (LS) amongst colorectal cancer (CRC) index patients to determine the efficacy (LS patients detected) of the experimental strategy testing CRC at 70 years or below (CRC≤70) versus current practice testing CRC at 50 years or below (CRC≤50). Numbers reflect the probability (mean±standard deviation as derived from literature, see online only S5) of the variable; # is the complementary probability (1-p).

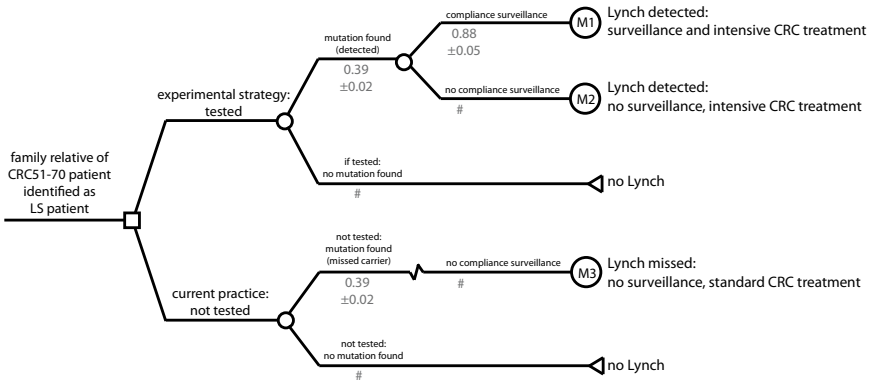

Figure 2: Family-based decision analytic model for identifying Lynch syndrome (LS) amongst relatives of patients with colorectal cancer (CRC) between 51-70 years identified as LS patients, either tested and detected by the experimental strategy or not tested and missed by current practice. Numbers reflect the probability (mean±standard deviation as derived from literature and local database, see online only S6) of the variable and # the complementary probability (1-p).

(intensive if tested in experimental strategy; standard if not tested in current practice) of a hypothetical cohort of CRC51-70 patients using stochastic data (means with standard deviations) to perform probabilistic sensitivity analyses (N=1000 Monte Carlo simulations). The third model (Figure 2) focused on cost-effectiveness in relatives of CRC51-70 patients identified as LS patients, with an integrated Markov model (S3b) for survival and surveillance (intensive if tested; none if not compliant or tested). First CRC in LS relatives non-compliant to surveillance, was assumed to be treated as LS-related. Future costs and effects were discounted at 4% to present values.[78] Acceptable cost-effectiveness threshold was €80,000 per life year gained, assumed equal to quality-adjusted life years.[79]

Cost data sources and assumptions

Costs per care unit are shown in S4. Procedures for genetic counseling, colonoscopy, CRC treatment and follow-up were considered unchanged from 2005[41]: costs were corrected for the Dutch consumer price index for healthcare.[80] Genetic testing costs have changed substantially thus were newly assessed (August 2013) locally. Average costs for DNA-analysis of index patients were based on pair wise testing of genes *MLH1/PMS2* or *MSH2/MSH6* (single DNA isolation processing). Average costs for DNA-analysis of relatives were based on gene distribution in a local database including all index LS patients diagnosed between May 1996 and August 2013 (N=182: *MLH1* 32%, *MSH2/EPCAM* 34%, *MSH6* 23%, *PMS2* 12%). Overhead costs (35.5%) were included.[78]

Patient data sources and assumptions

Data for patient-based models (S5) was based on a literature review, searching the PubMed database for MESH terms [Colorectal Neoplasms Hereditary Nonpolyposis AND Genetic Testing AND Aged AND Microsatellite Instability]. Search results were selected by year (2000-2013), publication language (English or Dutch), study design (prospective cohort studies of newly diagnosed CRC patients in populations similar to Dutch populations) and genetic testing including MSI (MSI-high: minimum 2 of 5 markers positive), IHC (four MMR genes), *MLH1* promoter hypermethylation (in MLH1-deficient tumours) and DNA-analysis, with separable data for CRC≤70 and CRC≤50. Four studies were included: two American[81,82], one Dutch[83] and one French.[84] Additional data was derived from our previous study[41] and several Dutch national databases.[77,80,85]

In literature, 96% of index LS patients comply with surveillance[58]; 100% compliance was assumed. Mortality rates of LS-related CRC[85] were assumed zero after 15 years and equal for first and second CRC tumours. Intensive CRC follow-up was defined as colonoscopy every two years; standard as every six years.[57] Yearly risks of a second CRC tumour following intensive versus standard CRC treatment in LS patients, were calculated using 10 year risks for subtotal versus partial colectomy in LS.[59] Age distribution of CRC 51-70 patients was derived from literature.[81-84] Markov chain analyses (S3a) were run for 30 years, considered a realistic timeframe given aforementioned age distribution and using age dependent Dutch mortality rates (2012).[80]

Family data sources and assumptions

Data for family-based models (S6) was based on a local database containing all relatives tested before August 2013 (N=935) of 112 index LS patients diagnosed between May 1996 and August 2011 (S7) allowing a minimum two years for relatives to undergo DNA-screening. Mean numbers of relatives tested (X) and identified as LS patients (Y) per index LS patient were calculated. Surveillance compliance amongst relatives was 88%.[86] Yearly risks of CRC for compliant and non-compliant LS patients were calculated from Järvinen et al.[9] Risks of LS-related CRC mortality and second CRC were assumed equal to index patients.[59] Markov chain analyses (S3b) were run for 50 years.[80]

RESULTS

Patient-based models

Using the experimental strategy, four times as many LS patients were identified than current practice. Costs and number needed to test for detecting one LS patient doubled (Table 1: €9,437/carrier versus €4,837/carrier and 42 versus 19). Within the age group of

Table 1: Efficacy (mean±standard deviation or [95% confidence interval]) of the identification of Lynch syndrome patients (mismatch repair gene mutation carriers) amongst patients with colorectal cancer (CRC), comparing the experimental strategy testing CRC at 70 years or below (CRC≤70) with current practice testing CRC at 50 years or below (CRC≤50).

Efficacy (all CRC patients)	Current practice: CRC ≤ 50	Experimental strategy: CRC ≤ 70	Difference (Δ) between strategies: CRC 51-70
% tested of all CRC patients	6.0	50.0	44.0
% MSI-high of those tested	11.9 ± 2.0	10.7 ± 0.8	10.4 ± 0.8
% *MLH1* promoter hypermethylation of those MSI-high	7.1 ± 3.4	46.9 ± 3.2	58.8 ± 3.6
% mutation detection rate (carriers / patients tested)	5.4	2.4	2.0
% identified as LS patient of all CRC patients	0.3	1.2	0.9
Number of CRC patients tested for MSI to detect one LS patient	19	42	50
Costs of genetic testing (€) per LS patient detected	4,837	9,437	11,541 [8,175 – 16,969]

CRC = colorectal cancer. MSI = microsatellite instability.

51-70 the incremental costs were €11,541 per additional LS patient detected. Mutation detection rate was lower in patients diagnosed at or below 70 versus 50 years (2.4% versus 5.4%). In additionally tested CRC 51-70, 58.8% of MSI-high tumours was due to *MLH1* promoter hypermethylation (not LS) versus 7.1% in CRC≤50.

Markov chain analyses of CRC 51-70 patients showed 0.01 extra life years gained versus current practice at incremental costs of €212, resulting in a ratio of €25,130 per life year gained (Table 2; S8).

Family-based model

With the experimental strategy, more CRC patients were identified as LS patient, leading to a proportionally increased number of relatives detected as additional LS patients. In our setting, every index LS patient led to genetic testing of on average 8 relatives (935 relatives of 112 index patients) of which 39% were LS patients (S6).

Markov chain analyses of relatives showed that the experimental strategy resulted in -€292 lower costs and 0.32 extra life year gained versus current practice (Table 2; S9). Therefore the experimental strategy was dominant over current practice, which would miss these LS relatives, denying them CRC surveillance.

Combined patient-family results

For an average LS family, the results of eight relatives were added to results of CRC 51-70 patients identified as LS (2.0%), resulting in an overall ratio of €2,703 per extra life year

Table 2: Cost-effectiveness (mean [95% confidence interval]) considering genetic testing and follow-up of index patients with colorectal cancer (CRC) between 51-70 years and genetic testing and surveillance in relatives, comparing the experimental strategy (patients with CRC 51-70 are tested: mutation detection rate 2%) and current practice (patients with CRC 51-70 are not tested).

Cost-effectiveness	Current practice: CRC between 51-70 are NOT tested for genetic susceptibility	Experimental strategy: CRC between 51-70 ARE tested for genetic susceptibility	Difference (Δ) between strategies: experimental - current
Patients with CRC 51-70			
Costs of genetic testing, cancer treatment and follow-up (€) [A]	24 [17 – 35]	236 [221 – 253]	212 [202 – 222]
Effect cancer treatment and follow-up: life years gained [B]	0.15 [0.10 – 0.22]	0.16 [0.11 – 0.23]	0.01 [0.01 – 0.01]
Costs (€) per life year gained [A / B]	160	1468	25,130 [16,362 – 36,999]
Relative of CRC 51-70 patient identified as LS patient			
Costs of genetic testing, surveillance and cancer treatment (€) [C]	1,725 [1,330 – 2,012]	1,434 [1,122 – 1,670]	-292 [-342 – -210]
Effect surveillance and cancer treatment: life years gained [D]	6.90 [5.29 – 8.15]	7.22 [5.51 – 8.59]	0.32 [0.21 – 0.45]
Costs (€) per life year gained [C / D]	250	199	*
Average family including CRC 51-70 patient and cascade screening of 8 relatives in patients identified as LS (2%)			
Costs of genetic testing, cancer treatment, follow-up, surveillance (€) [A + 2%*8*C]	300	465	165
Effect cancer treatment, follow-up, surveillance: life years gained [B + 2%*8*D]	1.25	1.32	0.06
Costs (€) per life year gained [(A + 2%*8*C) / (B + 2%*8*D)]	239	354	2,703

CRC = colorectal cancer.

* As demonstrated by lower costs with higher effects, the experimental strategy is dominant over current practice: thus accompanying (negative) cost-effectiveness ratio is not reported.

gained (Table 2) per additionally tested CRC 51-70 patient. Smaller family sizes of four or six relatives resulted in €5,301 or €3,659 per extra life year gained.

DISCUSSION

The experimental strategy for detecting Lynch syndrome is found to be cost-effective, as four times as many LS patients were detected for €2,703 per extra life year gained in additionally tested patients, including family cascade screening. This fourfold efficacy amongst index patients was achieved at only twice the cost (€9,437/carrier versus €4,855/carrier) and numbers needed to detect one carrier (42 versus 19), despite half of MSI-high CRC≤70 tumours being caused by non-hereditary *MLH1* promoter hypermethylation. In additionally tested CRC51-70 patients, the experimental strategy resulted in more costs for negligible survival gains (€25,130 per life year gained). But higher benefits were found in relatives using their LS knowledge for CRC prevention, resulting in a more favourable ratio of €2,703 per life year gained. Although the cost-effectiveness threshold of €80,000 in Dutch standards uses quality-adjusted life years[79] and our study used non-quality-adjusted life years, the experimental strategy seems good value for money. This recommendation could greatly improve the identification of Lynch syndrome, allowing more LS patients to prevent CRC mortality and simplifying the LS diagnostic process considerably. Half of all CRC patients would be tested immediately; only those with CRC>70 would require evaluation of other tumours and family history, lowering the burden on clinical genetic services. Such simplification may lead to high uptake at implementation of the new strategy.

To identify 100% of LS patients, testing all CRC patients could be considered.[87] But the diagnostic yield of testing without any age limit is comparable to testing only CRC≤70 and CRC>70 fulfilling Bethesda guidelines, with 35% fewer patients requiring tumour genetic testing and 29% fewer requiring DNA-analysis.[76] Testing without age limit compared to testing up to 50 years showed an incremental cost-effectiveness ratio of $37,010 per life year gained.[88] But Ladabaum et al[89] demonstrated rising costs with each 10-year increase: testing up to 60 versus 50 years cost $33,800 per life year gained; testing up to 70 versus 60 years cost $44,200 per life year gained; and testing all ages versus up to 70 years cost $88,700 per life year gained. Although gynaecological screening was included and genetic testing costs have decreased since 2011, this shows a trend for higher ratio's thus lower likelihood to be cost-effective by including CRC>70.

In our study, the experimental strategy led to only 0.01 extra life years gained in index patients due to higher average age of CRC 51-70 patients than CRC≤50 with higher

population mortality rates. This is comparable to Ladabaum et al[89]: Bethesda-based versus no testing led to 0.18 extra life years gained. In relatives, our study showed 0.32 extra life years were gained; lower than other conclusions that surveillance starting at 25 years gave 13.5 extra life years[90], as average age in our study was 45 years. But it remains evident that although index patients may not benefit greatly from improved LS identification, their relatives do.

The main strength of our study is the use of stochastic data for most input variables (S5-S6), allowing assessment of 95% confidence intervals, showing cost-effectiveness even at these upper limits. Several variables were based on a previous cost-effectiveness study[41] although different methods were used. The previous study compared two different strategies with full patient- and family-based criteria. The current study evaluated only the raised age limit from 50 to 70 years in one patient with one CRC tumour, not considering other tumours or family history. Those with CRC≤50 overlapped in both guidelines therefore cost-effectiveness analyses focused on the additionally tested CRC51-70 index patients, comparing costs and effects if LS patients within this group were tested (experimental strategy) or not tested (current practice). This may explain higher benefits in the family-based model, where CRC surveillance in additional LS patients detected led to lower costs and higher effects than if they were missed. The previous study only considered costs and effects in those detected (€855 per life year gained), not weighed against those missed.[41] Additional risks of a second CRC tumour[59] were incorporated, allowing more robust simulation of LS patient lifetimes and higher benefits than previous analyses only considering the first CRC tumour.[41]

Preference for MSI or IHC as first-pass LS testing is the subject of debate: sensitivity is equal, but IHC has the advantage of pinpointing which MMR genes to examine for germline mutations.[29] Conversely, IHC shows higher interobserver variability depending on observer experience, leading to preferred centralisation of IHC testing within specialised centres.[91] Thus MSI remained the gold standard for first-pass LS testing[57], determining our testing algorithm. Including the *MLH1* promoter hypermethylation test is important to detect non-hereditary MSI-high CRC (nearly half of CRC≤70) and minimise the proportion of patients undergoing expensive DNA-analysis.

The generalisability of our study results may be influenced by the assumptions made. Analyses were based on the Dutch healthcare system using MSI as first-pass LS testing, but MSI may be second to IHC elsewhere. MIPA criteria[42] are used in the Netherlands to select CRC≤50 patients for direct tumour genetic testing, but may not reflect current practice in other countries. Some family-based variables were calculated using a local and long-term database, not considering regional variances or degree of relatedness.

Cascade screening may – through initial screening of first/second degree relatives – reach third or more degree, leading to more relatives tested per family and fewer relatives identified as LS patients (in our setting 39%) than expected for close relatives (50%). Some LS patients amongst CRC patients may belong to the same family. Genetic testing costs were based on local data and may vary. However our main conclusion that increasing the upper age limit for MMR-deficiency testing from 50 to 70 is cost-effective is probably relevant for most western countries.

In conclusion, the proposed experimental strategy, testing all new CRC patients diagnosed at age 70 or below for Lynch syndrome, is more effective than current practice using an age limit of 50 years. Implementation is important as relatives from many LS patients missed by current practice, can benefit from life-saving surveillance.

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Chapter 3

DNA-testing for *BRCA1/2* prior to genetic counseling in patients with breast cancer: Design of an intervention study, DNA-direct

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ABSTRACT

Background: Current practice for patients with breast cancer referred for genetic counseling, includes face-to-face consultations with a genetic counselor prior to and following DNA-testing. This is based on guidelines regarding Huntington's disease in anticipation of high psychosocial impact of DNA-testing for mutations in *BRCA1/2* genes. The initial consultation covers generic information regarding hereditary breast cancer and the (im)possibilities of DNA-testing, prior to such testing. Patients with breast cancer may see this information as irrelevant or unnecessary because individual genetic advice depends on DNA-test results. Also, verbal information is not always remembered well by patients. A different format for this information prior to DNA-testing is possible: replacing initial face-to-face genetic counseling (DNA-intake procedure) by telephone, written and digital information sent to patients' homes (DNA-direct procedure).

Methods/design: In this intervention study, 150 patients with breast cancer referred to the department of Clinical Genetics of the Radboud University Nijmegen Medical Centre are given the choice between two procedures, DNA-direct (intervention group) or DNA-intake (usual care, control group). During a triage telephone call, patients are excluded if they have problems with Dutch text, family communication, or of psychological or psychiatric nature. Primary outcome measures are satisfaction and psychological distress. Secondary outcome measures are determinants for the participant's choice of procedure, waiting and processing times, and family characteristics. Data are collected by self-report questionnaires at baseline and following completion of genetic counseling. A minority of participants will receive an invitation for a 30 min semi-structured telephone interview, e.g. confirmed carriers of a *BRCA1/2* mutation, and those who report problems with the procedure.

Discussion: This study compares current practice of an intake consultation (DNA-intake) to a home informational package of telephone, written and digital information (DNA-direct) prior to DNA-testing in patients with breast cancer. The aim is to determine whether DNA-direct is an acceptable procedure for *BRCA1/2* testing, in order to provide customized care to patients with breast cancer, cutting down on the period of uncertainty during this diagnostic process.

Trial registration: The study is registered at the Dutch Trial Registry www.trialregister.nl (NTR3018).

Keywords

hereditary – breast cancer – BRCA – genetic – counseling – DNA

BACKGROUND

Patients with breast cancer at high risk of an underlying hereditary predisposition face a time-consuming diagnostic process of several months: it might be helpful to be able to cut down on this long period of uncertainty and provide information applicable to their personal situation as early as possible. Having personal experience with breast cancer, these patients are likely to have enhanced personal risk estimates, thus a higher expectation for protective actions such as longer or more intensive surveillance.[92] Should they carry a pathogenic mutation in either the *BRCA1* or *BRCA2* gene, these patients do have a considerable long term risk for developing a second primary breast cancer (either ipsi- or contralateral) of up to 60%.[31-33] Women recently diagnosed with breast cancer may want to take their *BRCA1/2* status into consideration for their choice of surgical treatment (i.e. breast-conserving with radiotherapy versus ipsi/contralateral mastectomy) and, in the near future, chemotherapy (i.e. PARP-inhibitors).[69,93-97] *BRCA1/2* mutation carriers face an additional risk of ovarian cancer ranging from 20-60% for *BRCA1* and 2-20% for *BRCA2*.[31-33] As screening for ovarian cancer through yearly serum CA-125 measurements and transvaginal ultrasound has proven to be ineffective[63,64,98], clinicians strongly recommend prophylactic bilateral salpingoophorectomy (pBSO) around the age of 35 to 40 years.[64] pBSO reduces the risk of ovarian cancer by 80-90%, and in unaffected premenopausal women simultaneously reduces breast cancer risk by 50%.[65,99]

Patients with breast cancer often express concern and uncertainty regarding the risk of breast cancer for their unaffected relatives, especially their sisters and daughters.[100] For unaffected relatives carrying a *BRCA1/2* mutation, cumulative breast cancer risk at the age of 70 years ranges from 40-80%.[31-33] At the age of 25 years, they may choose between an intensive breast cancer screening program consisting of yearly MRI scans, mammography and clinical breast examinations[101,102] or undergoing prophylactic surgery, reducing the risk for breast cancer by 90%.[10,103,104] Some carriers may still be at an age to be confronted with childbearing conflicts.[66] These are only a few of the life-changing decisions for both patients with breast cancer and their relatives dependent on the results of DNA-testing, which may or may not confirm the presence of a genetic predisposition for breast and ovarian cancer. A previous study in Dutch patients being evaluated for possible breast cancer showed that these patients experienced the period before the final diagnosis as the most stressful, regardless of whether they had received a benign or cancer diagnosis afterwards.[105] This same principle likely applies to *BRCA1/2* testing. Reducing the period of uncertainty in the diagnostic process and offering various forms of information might help substantially.

Another attempt to speed up the diagnostic process concerning hereditary cancer was previously introduced in the evaluation of hereditary colon cancer in the Netherlands. Pathologists are now able to test tumor material of patients younger than 50 years for microsatellite instability (MSI) and immunohistochemical staining of gene products, which may reveal a high a priori risk for an underlying genetic predisposition, without prior consultation of a genetic counselor. If these characteristics are present, patients are referred for further evaluation by a genetic counselor.[41,106] This so-called MIPA procedure (MSI-test by pathologists) is seen by patients as a valuable addition to the diagnostic process of hereditary colon cancer, without feeling either overwhelmed or underinformed, nor showing increased levels of psychosocial distress.[43,107,108]

Such an intervention may also be applicable to patients with breast cancer. As there is no equivalent of tumor material testing in hereditary breast cancer, alternatives for modification must be found within the current diagnostic process. Genetic testing for hereditary breast cancer includes genetic counseling both prior to and following DNA-testing, based on guidelines regarding presymptomatic testing for Huntington's disease (HD).[109-111] This approach had been adopted for hereditary breast cancer due to concerns about the psychological consequences of *BRCA1/2* genetic susceptibility testing.[8] However, extensive prior research shows there is no significant long term psychological impact: after an initial increase following *BRCA1/2* testing, psychosocial distress returns to pre-testing levels over time.[112-118] Therefore, in the case of hereditary breast cancer where protective measures are possible, it may not be necessary to adhere to such a strict counseling protocol as defined for an untreatable neurodegenerative disorder such as HD.[8] Patients with breast cancer express the most interest in answers regarding their personal situation: Is my breast cancer of hereditary origin and what are my children's risks?[119] Answers to these questions cannot be given until the results of DNA-testing are known. During the initial face-to-face consultation, patients are provided with general information regarding hereditary breast cancer, DNA-testing and possible consequences, prior to actual DNA-testing. Patients consider this generic information less relevant than the personal advice in the second consultation post DNA-testing and may thus experience this intake as an unnecessary delay.[120] It is also widely known that about 40 to 80% of verbal information is immediately forgotten by patients.[121] A recent study in Canada offered a group of Jewish women DNA-testing through written and telephone invitation. The majority of these women had positive experiences with this approach and considered it to be effective.[122] Providing patients with alternative means to educate themselves regarding hereditary breast cancer and DNA-testing, prior to their decision to undergo testing, might improve patient recollection of medical information as well as increase patient participation.

Therefore, this study offers patients with breast cancer the choice of replacing the initial face-to-face consultation prior to DNA-testing (usual care DNA-intake procedure) by a home information package including telephone, written and digital information consisting of a website and educational movie (DNA-direct procedure). DNA-testing will thus be performed prior to genetic counseling, contrary to current practice. At the first face-to-face contact, counselors will be able to disclose DNA-results and customized advice to patients. This eliminates extraneous information which is not applicable to the individual patient, and provides patients with the information they desire in a quick and patient-centric manner.

The aim of this intervention study is to compare this new DNA-direct procedure to current practice (DNA-intake procedure). The effects of the DNA-direct procedure on the experience and psychosocial distress on patients with breast cancer, as well as the speed and quality of genetic advice, will be evaluated. The hypothesis is that undergoing the DNA-direct procedure does not lead to increased levels of psychosocial distress as compared to the usual care DNA-intake procedure, with equal levels of patient satisfaction plus shorter waiting and processing times. A trend similar to traditional *BRCA1/2* testing – a short term increase in distress, falling back to pre-testing levels over time[112-118] – is expected in the DNA-direct procedure. This would make DNA-direct an acceptable procedure for patients with breast cancer undergoing genetic testing, with the goal of more customized care, and a shorter period of uncertainty. Moreover, it would facilitate taking genetic advice into account for the treatment and follow-up of breast cancer.

METHODS/DESIGN

Design

The study examines the effect of the DNA-direct procedure on the experience and psychological distress of patients with breast cancer as well as several secondary outcome measures, including waiting and processing times, as compared to the current DNA-intake procedure. Two groups will be compared: the intervention group, who choose to undergo the DNA-direct procedure, and the control group, who will receive care as usual (DNA-intake procedure). Participants may choose freely between the DNA-direct versus DNA-intake procedures. This study is not randomized due to the wish to evaluate whether there is indeed a desire for the proposed DNA-direct procedure amongst patients with breast cancer, and to evaluate the reasons stated for preferring one procedure over the other.

Ethical consideration

The study has been approved by the medical ethical committee of the Radboud University Nijmegen Medical Centre. Full medical ethical approval has been obtained in July 2011.

Study sample

All female patients previously or currently diagnosed with breast cancer and referred to the department of Clinical Genetics of the Radboud University Nijmegen Medical Centre from August 9th 2011 are eligible for inclusion. Recruitment will continue until the desired total of 150 participants is reached. Patients who have problems reading Dutch text, problems with family communication or problems of psychological/psychiatric nature (including current use of related medication) will be excluded.

Recruitment

Patients are sent a written letter by a trained doctor announcing a phone call, in which the two choices of procedure are explained (DNA-intake for a face-to-face intake consultation prior to DNA-testing, versus DNA-direct for a home package of telephone, written and digital information) and exclusion criteria are checked. The aim of this telephone approach is triage: by checking for exclusion criteria such as psychological problems, patients who aren't deemed suitable for DNA-direct (due to its dependency on the patient's own decision making ability) are filtered out and instead invited for a regular intake consultation, where further psychosocial support is immediately available prior to DNA-testing. Genetic counseling is not offered by phone: questions of this nature are deferred to the personal consultations. The triage phone call has been thoroughly practiced (over 20 times) by the involved doctor with people both specialized and not specialized in clinical genetics.

All patients receive the same two questionnaires, one at inclusion (baseline) and one after completion of the chosen genetic counseling procedure (follow-up). Patients who are confirmed carriers of a *BRCA1/2* mutation, patients reporting problems with the chosen procedure, and randomly selected (n = 10) patients will be invited for a 30 min semi-structured telephone interview.

BRCA1 and *BRCA2* genetic testing

The coding sequences and intron/exon boundaries of *BRCA1* and *BRCA2* are analyzed by sequence analysis (primer sequences available on request). Gross deletions and duplications in the *BRCA1* gene are detected by multiplex ligation-dependent probe amplification (MRC-Holland, Amsterdam, kit P002-C2). All findings are confirmed by an independent test.

Intervention

Patients who choose the DNA-direct procedure, receive a home informational package including an informational letter, a link to a website including a short educational movie about hereditary breast cancer and DNA-testing. Also included are two EDTA blood vials with informed consent and family history forms. Patients are instructed to call their family doctor assistant to ask where to have their blood drawn, then return the vials plus signed forms in the appropriate return package. An appointment for a personal consultation to disclose results is set 8 weeks after DNA-testing has commenced.

All patients (whether they choose DNA-direct or DNA-intake) are seen by one of five selected genetic counselors, each of whom has extensive experience in genetic counseling for hereditary cancer. These counselors have had multiple meetings in order to structure the DNA-direct consultations as follows: If no mutation is found, further screening advice is formulated based on familial risk scores: FHAT[123], Myriad[124] and Claus/van Asperen.[125,126] Further evaluation of family history and features of other hereditary cancer syndromes may be required. In the case of a pathogenic *BRCA1* or *BRCA2* mutation, this result is disclosed immediately, first allowing the patient to react, followed by an explanation of the consequences, including prevention measures and family evaluation. If considered necessary, a second consultation is offered for further genetic counseling. All confirmed *BRCA1/2* carriers will be approached by a social worker to extend psychosocial support if needed, as in usual care.

Study outcomes

Participants are asked to fill out a questionnaire twice: at baseline and following the conclusion of genetic counseling and/or testing (follow-up). Some measures are used in both questionnaires, while others are only included in either baseline or follow-up.

Primary outcomes

Choice of procedure

Percentages of patients choosing one procedure over the other (ratio between the two groups) is determined to assess the desirability of the new DNA-direct procedure.

Psychological burden (baseline and follow-up)

Quality of Life

To measure global health-related quality of life (QoL), two items scored on a scale of 1–7 were selected from the EORTC-Q30. The full EORTC-Q30 has been widely used and

validated for cancer research.[127] The two global QoL items have an excellent internal consistency as proven by the reported Cronbach's α of 0.91.[128]

General health

The 12-item version of the General Health Questionnaire (GHQ-12) is used as a measure of general psychological distress, using GHQ-scoring of 0,0,1,1 per item (range 0–12) with a threshold of ≥4 to identify 'caseness', recommended for patients with breast cancer. The GHQ-12 is the shortest version of all GHQs and recommended for research use, with good internal consistency (Cronbach's α = 0.82 - 0.86).[129-131]

Cancer specific distress

The Impact of Event Scale (IES) measures cancer specific distress[132,133] and is included in baseline once using genetic predisposition for cancer as the distressing event, once using breast cancer. For follow-up, only genetic predisposition is included. The IES consists of 15 items, each scored 0,1,3,5. A total score of 9–25 or ≥26 reflects moderate or serious adaptation difficulties respectively. The Dutch version of the IES has a good internal consistency with a Cronbach's α of 0.87 to 0.96.[133]

Risk perception

Risk perception of a genetic predisposition for breast cancer, as well as breast cancer recurrence, is measured on a scale of 0–100.

Cancer worry scale

To measure fear of cancer recurrence, the 8-item Cancer Worry Scale (CWS) is included, which has previously been used in studies among cancer patients. Each item is scored 1,2,3,4 from 1 'almost never' to 4 'almost always', the total score ranging from 8–32. It has a good internal consistency with a Cronbach's α of 0.80.[134-136]

Experiences with genetic counseling (follow-up)

Decisional conflict

The difficulty of decision-making, in this study defined as whether or not to undergo genetic testing, is assessed using the traditional format of the Decisional Conflict Scale; 1 item ("I expect to stick to my decision") is left out as it is not applicable to DNA-testing.[137-139] 15 items scored 0,1,2,3,4 from 0 'strongly agree' to 4 'strongly disagree' remained, including "I am satisfied with my decision" which is also used separately for overall satisfaction. Scores are summed, divided by 15 and multiplied by 25, resulting in a range from 0 to 100. Scores below 25 are considered as 'no decisional conflict', between 25 and 37.5

as 'moderate conflict' and exceeding 37.5 as 'severe conflict'. The DCS has good internal consistency exceeding 0.78.[137-139]

Satisfaction with choice

Knowledge of hereditary breast cancer following versus prior to the chosen genetic counseling procedure, as well as the amount and quality of information received, is rated on a scale of 1–6. Participants answer 'yes', 'no' or 'don't know' for choosing DNA-testing and/or DNA-direct if given a second chance or asked to give advice to other women in a similar situation.

Satisfaction with genetic counseling

QUOTE-gene(ca) is a standard Dutch questionnaire to measure patient satisfaction with the service (18 items) and information (8 items) expected of a genetic counselor.[140] Each item is scored on a Likert-scale 1–4, total scores range from 26–104. Open-ended questions evaluate positive/negative experiences during the chosen genetic counseling procedure.

Secondary outcomes

General information (baseline)

Demographical and breast cancer information

Data are gathered on age, education level, work status, marital and parental status, cancer status, medical information need (scale 1–10), use of breast cancer information resources and type of information previously given by their referring physician.

Empowerment (baseline)

Empowerment is the process in which patients discover and utilize their own power, which will be measured using the Cancer Empowerment Questionnaire (CEQ). It consists of 40 items, each scored on a Likert-scale of 1–5 (1 'strongly disagree', 5 'strongly agree'). Four factors are identified: 'Personal Strength', 'Social Support', 'Community' and 'Health Care'. A good internal consistency (Cronbach's $\alpha = 0.94$) was demonstrated for all four factors and the total Empowerment scale.[141]

Experiences with genetic counseling and testing (follow-up)

Choice of procedure

Participants describe reasons for choosing DNA-direct or DNA-intake.

Family relations

Three categories of family members are defined: 1) nuclear family, being partner and/or children; 2) family of origin, being parents, brothers and/or sisters; and 3) aunts and female cousins on the family side where breast cancer is prevalent, being the second generation relatives most likely to be affected by genetic testing of the patient. Participants report the frequency of contact with each category of relatives, as well as indicate the quality of their relationship on a scale of 1–10.

Family communication

For each above-mentioned relative, participants indicate whether, and if so, when (directly after information, just before DNA-result, after DNA-result) and how often (on a scale of 1–5), they had spoken to this relative about hereditary breast cancer. Also included is the Openness to Discuss Hereditary Cancer in the Family scale (ODHCF) which consists of 7 items each scored 1,2,3,4 with a range 7–24: once for the nuclear family ($\alpha = 0.79$) and once for the family of origin ($\alpha = 0.93$).[142]

Other measures

Waiting and processing times, as well as family pedigree characteristics, are also gathered.

Sample size calculation

For this intervention study, participants are not randomized into groups, but given their own choice. This leads to certain complications when it comes to a formal power calculation. First, the ratio between the two procedures is unknown: this may either be balanced (50% versus 50%) or unbalanced (e.g. 20% versus 80%). Second, due to not randomizing, the results will have to be corrected for multiple confounders, which are not all known at this point. The sample size, based on aforementioned ratio between both groups (choice of procedure), needs to be large enough to be able to integrate these confounders into a regression model. Using a power of 80% and a two-tailed probability level for statistical significance testing of 0.05, while taking into account group ratios ranging from balanced (50% versus 50%) versus unbalanced (to an estimated maximum of 20% versus 80%), the total sample size has been set to 150 patients with breast cancer.

Statistical analyses

To compare general characteristics, baseline and follow-up results between the intervention versus control group, the unpaired t-test will be used for continuous variables, Mann–Whitney U test for non-parametric variables and chi-square test for dichotomous variables. For the comparison of baseline versus follow-up results within each group, the paired t-test will be used for continuous, Wilcoxon test for non-parametric

and McNemar's test for dichotomous variables. Multivariate analysis will consist of a regression model using the follow-up results as outcome (dependent) variables, to be compared between the intervention versus control groups as independent variables, with the baseline results as covariates supplemented by variables that were found to be statistically significant in previous univariate analyses. The probability level for statistical significance testing is set at 0.05 (two-tailed). The SPSS 18.0 statistical package will be used to analyze the data.

DISCUSSION

Considering today's call for more patient participation in medical decision-making, the convenience of taking up information and drawing blood close to home, paired with customized advice from the very first consultation, might appeal to patients. Replacing the face-to-face intake consultation with a genetic counselor by a home informational package of telephone, written and digital information might speed up the diagnostic process of hereditary breast cancer and reduce extraneous information. For example, this would allow patients to go over this information at their own convenience and in their own homes. It could possibly reduce travel efforts to a hospital as well as time conflicts with breast cancer therapy.

However, there are certain downsides compared to traditional genetic testing. All patients with breast cancer referred to clinical genetics by their treating physician are eligible for the DNA-direct procedure. This means that even those patients who would not normally fulfill criteria for *BRCA1/2* testing are now able to have their blood drawn for DNA-testing, regardless of those criteria. In the DNA-intake procedure, patients who do not fulfill the aforementioned criteria will not be offered further DNA-testing. This may lead to a selection bias. Our intention is to compare DNA-direct to current practice: adhering to these criteria is the current practice and must be reflected in the DNA-intake procedure.

Additionally, genetic counselors must adjust their counseling styles to the disclosure of the DNA-results being the first order of business, without having built up a counselor-patient relationship beforehand. New information might come forward following result disclosure, leading to ad-hoc modification of screening advice. For this reason, as well as to avoid intercounselor variation, we have selected five genetic counselors with many years of experience in oncogenetic counseling to see all patients participating in this study (both DNA-direct and DNA-intake).

In conclusion, the aim of our study is to determine whether DNA-direct is an acceptable procedure for *BRCA1/2* testing, in order to provide customized care to patients with breast cancer and remove unnecessary waiting times within the diagnostic process, cutting down on the long period of uncertainty that patients are currently faced with.

COMPETING INTERESTS

The authors declare that they have no competing interests.

Authors' contributions

NH and JBP have contributed to the study protocol and revised the manuscript. ASS has contributed to the study protocol and wrote the manuscript. LS, WAGZS, ARM, MJL and HGB have contributed to the study protocol. All authors have read and approved the final manuscript.

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Chapter 4

More breast cancer patients prefer *BRCA*-mutation testing without prior face-to-face genetic counseling

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ABSTRACT

Currently, most breast cancer (BC) patients receive face-to-face genetic counseling (DNA-intake) prior to *BRCA*-mutation testing, with generic information regarding hereditary BC and *BRCA*-mutation testing. This prospective study evaluated a novel format: replacing the intake consultation with telephone, written and digital information sent home, and face-to-face contact following *BRCA*-mutation testing (DNA-direct). From August 2011 to February 2012, 161 of 233 eligible BC patients referred to our Human Genetics department chose between DNA-direct (intervention) or DNA-intake (control). Exclusion criteria were psychological problems (n=33), difficulty with Dutch text (n=5), known *BRCA*-family (n=3), non-*BRCA*-referral (n=1). 30 declined genetic counseling or study participation. Participants received questionnaires including satisfaction and psychological distress. 59% chose DNA-direct (p=0.03), of whom 90% were satisfied and would choose DNA-direct again (including 6/8 *BRCA*-mutation carriers); although 27% hesitated to recommend DNA-direct to other patients. General distress (GHQ-12, p=0.001) and heredity-specific distress (IES, p=0.02) scored lower in DNA-direct than DNA-intake, both at baseline and follow-up two weeks after *BRCA*-result disclosure; all scores remained below clinical relevance. DNA-direct participants reported higher website use (53% vs 32%, p=0.01), more referrer information about personal consequences (41% vs 20%, p=0.004) and lower decisional conflict (median 20 [0–88] vs 25 [0–50], p=0.01). Processing time in DNA-direct was reduced by one month. Mutation detection rate was 8% in both groups. All *BRCA*-mutation carriers fulfilled current testing criteria. In conclusion, more BC patients preferred DNA-direct over intake consultation prior to *BRCA*-mutation testing, the majority being strongly to moderately satisfied with the procedure followed, without increased distress.

Keywords

BRCA – breast cancer – counseling – DNA – genetic – hereditary

INTRODUCTION

Patients with breast cancer (BC) desire answers about their personal situation when considered at risk of a hereditary predisposition.[119] Providing personalized information as early as possible and reducing the long period of uncertainty during the genetic diagnostic process may prove helpful. In BC patients, a pathogenic *BRCA1/2*-mutation increases the risk of a second primary BC up to 60%[31-33] and may influence the choice of BC treatment.[96] The risk of ovarian cancer is also elevated to 20-60% for *BRCA1* and 2-20% for *BRCA2*[31-33] for which prophylactic surgery is recommended.[64] BC patients are often concerned about the BC risk for their relatives[100]: unaffected *BRCA1/2*-mutation carriers have a cumulative BC risk (to age 70 years) of 40-80%.[31-33] At 25 years, they are offered yearly BC screening or prophylactic surgery.[10] Patients experience the time between BC suspicion and diagnosis as the most stressful, independent of a benign or malignant outcome.[105] This likely applies to *BRCA*-mutation testing as well. Reducing the period of uncertainty and offering various forms of information might help.

Current practice in many countries involves face-to-face counseling both prior to and following *BRCA*-mutation testing, based on guidelines regarding Huntington's disease.[8] Such a strict protocol seems unnecessary for patients with BC as extensive research shows no long term psychological distress after *BRCA*-mutation testing.[12] This study offered BC patients the choice of replacing the initial face-to-face consultation prior to *BRCA*-mutation testing (usual care, DNA-intake procedure) by telephone, written and digital information with a blood drawing kit sent home (novel format, DNA-direct procedure). Such a combination may be preferred over a face-to-face intake consultation, since patients may forget 40-80% of verbal information in medical consultations.[121] Furthermore, *BRCA*-mutation testing was performed prior to genetic counseling, allowing counselors to disclose *BRCA*-results plus personalized advice at first face-to-face contact, eliminating extraneous information not applicable to each individual. Previous experience with genetic testing prior to genetic counseling, concerning tumor material in colorectal cancer patients younger than 50 years, showed that patients considered this as valuable without feeling underinformed or highly distressed.[43,106]

The aim of this study is to compare the experience of BC patients (satisfaction and psychological distress) between the novel DNA-direct procedure and usual care (DNA-intake). The hypothesis is that DNA-direct is preferred by BC patients undergoing *BRCA*-mutation testing with equal levels of patient satisfaction and no increased psychological distress.

PATIENTS AND METHODS

The complete protocol of this study was previously published, including full psychometric details of standardized questionnaires used.[143] In short, following approval by the local medical ethical committee in July 2011, all female patients (previously) diagnosed with BC and referred to our department of Human Genetics between August 2011 and February 2012 (n=233) were eligible (Figure 1). To evaluate whether there is a preference for DNA-direct, BC patients were free to choose between procedures. Patients were excluded if they reported psychological problems requiring professional counseling (n=10), medication (n=14) or advice to start treatment (n=9); if they had difficulty with Dutch text (n=5) or family communication (n=0), a known family *BRCA*-mutation (n=3) or were not referred for *BRCA*-mutation testing (n=1). 11 patients declined genetic counseling/testing. 180 patients were sent baseline (T0) self-report surveys in both procedures,

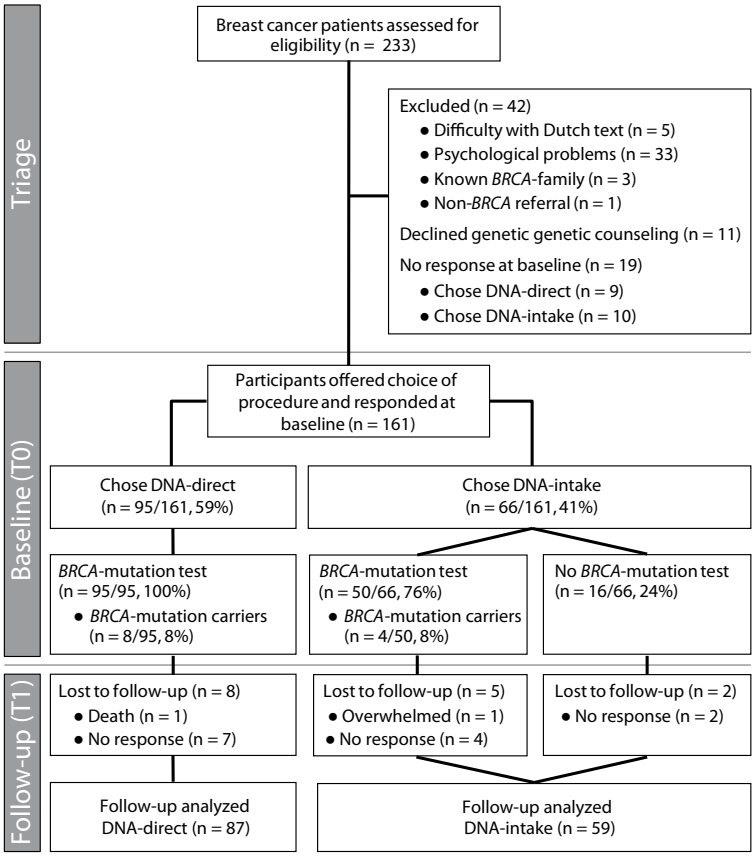

Figure 1: CONSORT flowchart of patient inclusion and follow-up, procedure proportions and *BRCA*-results.

returned by 161. Follow-up surveys were sent two weeks after *BRCA*-result disclosure (T1). A minority of patients were invited for a short semi-structured telephone interview (i.e. all *BRCA*-mutation carriers, 10 randomly selected non-*BRCA*-mutation carriers per group). Written interview notes were reviewed for common trends.

DNA-direct procedure

In the novel DNA-direct procedure, patients received telephone (triage call by a trained medical doctor), written and digital information (website, educational movie) at home, containing the same information usually covered in DNA-intake in both written and digital formats. A blood drawing kit was included to start *BRCA*-mutation testing; written informed consent for DNA-direct and family history forms were mandatory. Telephone or e-mail contact with the involved doctor were possible for questions. *BRCA*-results were disclosed in a face-to-face consultation. Further details were previously published.[143]

Study outcomes

Primary study outcomes were: ratio between participants choosing DNA-direct versus DNA-intake (To), satisfaction (T1: regarding choice of procedure, genetic counseling, information and *BRCA*-mutation testing, e.g. QUOTE-gene(ca)[119,140] average of 26 items on scale 1 'not at all' to 4 'good', Cronbach's α=0.96), and psychological distress (To/T1: general distress (GHQ-12[129] scale 0–12, α=0.84–0.89) and heredity-specific (IES[132,133] scale 0–75, α=0.93–0.94)). Full psychometric details of these standardized measures were previously published.[143] Secondary psychological outcomes measured at both To and T1 were in short: global quality of life (selected from EORTC-QLQ-Q30[127] scale 0–100, α=0.84–0.85), BC worry (CWS[134,135] scale 8–32, α=0.84–0.85), risk perception of hereditary BC and 2nd BC (visual scales 0-100). Other secondary To outcomes were: sociodemographics, patient and family history of breast/ovarian cancer, BC information use, decisional conflict (DCS[137,139] scale 0–100, α=0.96), patient empowerment (CEQ[141] scale 40–200, α=0.94), BC-specific distress (IES[132,133] α=0.93). Other secondary T1 outcomes were: open-ended reasons for choice of procedure, processing time, mutation detection rate, family relations and communication (e.g. ODHCF[142] two subscales 1–7, α=0.84–0.90). Further details of standardized measures were previously published.[143]

Sample size and statistical analysis

Sample size was based on the ratio between DNA-direct versus DNA-intake. A total of 150 participants was considered necessary to account for this unknown ratio, ranging from balanced (50% versus 50%) versus unbalanced (to an estimated maximum of 20% versus 80%), using a power of 80% and a two-tailed probability level for statistical significance testing of 0.05. Data is presented using descriptive statistics. To compare DNA-direct versus DNA-intake for each To and T1 outcome, the unpaired t-test was

used for continuous, Mann-Whitney U test for non-normally distributed continuous or ordinal and chi-square/Fisher's Exact test for nominal/dichotomous variables. Multiple backward (Wald) logistic regression was performed to analyze 1) the influence of multiple To variables differing significantly between DNA-direct versus DNA-intake in univariate analyses, and 2) clinical variables concerning personal and family cancer history as possible predictors of the choice of DNA-direct. Significant To differences were also corrected for in multivariate analyses (multiple linear/logistic regression) of T1 outcomes showing significant univariate differences. Repeated measurements ANOVA was used to test for changes over time (T1-To) between DNA-direct versus DNA-intake in psychological outcomes (general distress, heredity-specific distress, quality of life, BC worry and risk perception of hereditary BC and 2nd BC), with statistical correction for To differences as covariates. The SPSS 20.0 statistical package was used for analysis.

RESULTS

A total of 161 BC patients (Figure 1) was included. Patient characteristics are shown in Table 1. Most participants (66% of DNA-direct, 71% of DNA-intake) were included within one year following their last BC diagnosis. More patients chose the novel DNA-direct procedure versus DNA-intake (n=95; 59% and n=66; 41%, p=0.03).

Eight To patient characteristics were found to differ significantly between groups (marked * in Table 1). DNA-direct participants showed a higher education level (p=0.01), lower age of onset in their youngest BC-affected relative (p=0.03), more children living at home (p=0.03), more website use for BC information (p=0.01), more previous information about personal consequences of hereditary BC (p=0.006) and about possible outcomes of genetic testing (p=0.03). DNA-intake participants had been previously informed more about genetics in general (p=0.008) and showed higher decisional conflict (p=0.001). In multivariate analyses, only four of these variables remained significant contributors to the choice of DNA-direct over DNA-intake. Participants who had previously received information about personal consequences of hereditary BC (p=0.004, OR 3.46 [1.49–8.04]) or used websites for BC information (p=0.01, OR 2.75 [1.25–6.04]), were more likely to choose DNA-direct. Those who had received information about genetics in general (p=0.008, OR 0.35 [0.16–0.76]) or experienced higher decisional conflict (p=0.007, OR 0.96 [0.93–0.99]) were more likely to choose DNA-intake. This model was statistically significant with $\chi 2$ (4, n=145) = 30.61 (p<0.001) explaining 26% of the variance and correctly classifying 72% of cases.

Table 1: Baseline sociodemographic and breast cancer (BC) characteristics for all BC patients choosing either DNA-direct (novel format) or DNA-intake (usual care).

Characteristic	DNA-direct n=95: N (%) or median [range] or mean±SD	DNA-intake n=66: N (%) or median [range] or mean±SD	P
Age at inclusion	49 [23-73]	53 [28-74]	*0.10*
Age at 1st BC diagnosis	47 [23-71]	49 [28-74]	*0.15*
Months since last BC	6 [0-247]	6 [0-195]	*0.92*
***BRCA* referral criteria**			
- positive family history	75 (79%)	53 (80%)	*1.00*
- age at BC <40yrs	29 (31%)	13 (20%)	*0.15*
- ovarian cancer in patient	4 (4%)	2 (3%)	*1.00*
Family characteristics			
- mother with BC	17 (18%)	13 (20%)	*0.84*
- sister with BC	17 (18%)	15 (23%)	*0.55*
- age (yrs) youngest with BC	40 [23-62]	42 [26-64]	*0.03 **
- children living at home	55 (58%)	26 (39%)	*0.03 **
Educational level			*0.01 **
- high	39 (41%)	13 (20%)	
- medium	27 (28%)	25 (38%)	
- low	29 (31%)	28 (42%)	
Use of BC information sources			
- member of patient organization	6 (6%)	3 (5%)	*0.74*
- websites	50 (53%)	21 (32%)	*0.01 **
- online discussion forums	12 (13%)	3 (5%)	*0.10*
- newspaper	57 (60%)	39 (59%)	*1.00*
- TV	48 (51%)	32 (49%)	*0.88*
- physician: flyers	63 (66%)	45 (68%)	*0.87*
- physician: consultations	56 (59%)	28 (42%)	*0.05*
Information provided by referrer			
- genetics in general	25 (26%)	31 (47%)	*0.008 **
- hereditary cancer	38 (40%)	23 (35%)	*0.62*
- personal consequences	39 (41%)	13 (20%)	*0.006 **
- family consequences	38 (40%)	26 (39%)	*1.00*
- procedure of genetic testing	35 (37%)	17 (26%)	*0.17*
- outcomes of genetic testing	32 (34%)	12 (18%)	*0.03 **
Decisional conflict (DCS: 0-100)	*n=87:* 16.2±13.9	*n=58:* 23.2±10.8	*0.001 **
Empowerment (CEQ: 40-200)	*n=92:* 161.7±13.1	*n=63:* 159.8±16.0	*0.90*
BC specific distress (IES: 0-75)	*n=92:* 18.5±15.7	*n=64:* 22.8±17.1	*0.11*

* Statistically significant p<0.05: baseline differences included as covariate in multivariate follow-up T1and repeated measurements analyses.

To identify clinical predictors for the choice of DNA-direct over DNA-intake, eight personal and family cancer history variables (age at first BC diagnosis, months since last BC, positive family history, age at BC <40 years, ovarian cancer in patient, mother with BC, sister with BC and age of youngest BC-affected relative) were included in separate mul-

tivariate analyses. Only the age of youngest BC-affected relative remained a significant contributor (p=0.04, OR 4.38 [0.92–1.00]), as previously established.

Follow-up

All DNA-direct participants (n=95) were tested for *BRCA*-mutations. 76% (50/66) of DNA-intake participants were tested as they were only offered *BRCA*-mutation testing if they fulfilled international guideline selection criteria[61] although testing was possible on the patient's persistent request. Costs of genetic testing were covered by basic compulsory insurance. *BRCA*-mutation detection rate was equal at 8% for both groups: 8 *BRCA*-mutation carriers in DNA-direct and 4 in DNA-intake (one unclassified variant type III). Follow-up (T1) data is available of 87 DNA-direct (92%) and 59 DNA-intake (89%, p=0.78) participants, including 7 DNA-direct and 3 DNA-intake *BRCA*-mutation carriers. One DNA-direct *BRCA*-mutation carrier died before *BRCA*-result disclosure. One DNA-intake *BRCA*-mutation carrier felt overwhelmed by her *BRCA*-result from rapid genetic testing due to upcoming BC surgery and dropped out of the study.

Satisfaction with choice of DNA-direct

The majority (89%) of DNA-direct participants would choose DNA-direct again, including 6 *BRCA*-mutation carriers; one carrier retrospectively preferred DNA-intake due to the unexpected suspicion of an unrelated syndrome. Most (70%) DNA-direct participants, including 2 *BRCA*-mutation carriers, would also recommend DNA-direct to other BC patients; 27% (including 5 *BRCA*-mutation carriers) was uncertain. Three of these participants specified why: they would like every next participant to make their own individual choice.

Satisfaction with genetic counseling and information

Overall counseling services were considered sufficient (scale 1–4, median 3 [1–4]). Satisfaction with information (scale 1–6) was good at 5 [1–6] and 97% considered the amount of information sufficient (14%) or good (83%), with good quality (scale 1–6, 5 [2–6]). Self-evaluation of knowledge about hereditary BC post-counseling was good (scale 1–6, 5 [1–6]). Satisfaction was equal in DNA-direct versus DNA-intake.

Satisfaction with *BRCA*-mutation testing

53% of DNA-direct participants reported strong and 45% moderate satisfaction with their choice to start *BRCA*-mutation testing, versus 31% strong and 61% moderate satisfaction in DNA-intake participants (p=0.01). However, fewer DNA-direct than DNA-intake participants would start *BRCA*-mutation testing again if given a second chance (72% versus 95%, p=0.002). In DNA-direct, 9% (versus 5% in DNA-intake) was uncertain and 19% (versus 0%) would not start *BRCA*-mutation testing again. No reasons were

reported. 65% of DNA-direct versus 86% of DNA-intake would advise *BRCA*-mutation testing to other BC patients (p=0.01); respectively 28% versus 13% was uncertain. Four participants (n=2 DNA-direct, n=2 DNA-intake) indicated that each person must make their own choice. Adding fulfillment of *BRCA*-mutation testing criteria to multivariate regression analyses did not show a significant contribution of this variable (p=0.70) nor change the statistical significance of DNA-direct.

Psychological distress

As shown in Table 2, lower scores at baseline as well as at follow-up in DNA-direct versus DNA-intake were found for both general distress (GHQ-12: F(1,135)=10.80, p=0.001) and heredity-specific distress (IES: F(1,127)=5.97, p=0.02). Neither interaction between time and choice of procedure nor main effect for time were found. In both groups, mean scores remained below thresholds for clinical relevance (GHQ-12≥4 and IES≥26).

Secondary psychological outcomes

Quality of life, BC worry, risk perception for hereditary BC and 2nd BC did not differ between DNA-direct versus DNA-intake or over time (Table 2).

Table 2: Psychological measures (mean±SD) for all breast cancer (BC) patients choosing DNA-direct (novel format) or DNA-intake (usual care).

Characteristic	T0		T1		T1-T0		
	DNA-direct: n=95	DNA-intake: n=66	DNA-direct: n=87	DNA-intake: n=59	DNA-direct: n=87	DNA-intake: n=59	P
General distress (GHQ-12: 0-12)	3.2 ±3.1	3.9 ±3.2	2.7 ±3.4	3.6 ±3.5	-0.5 ±3.4	-0.3 ±4.2	*0.001*
Heredity specific distress (IES: 0-75)	12.9 ±14.2	17.2 ±16.1	11.7 ±13.3	16.7 ±17.2	-1.3 ±15.1	2.0 ±16.2	*0.02*
Quality of Life (QoL: 0-100)	73.7 ±18.6	72.6 ±16.5	74.2 ±17.5	73.0 ±15.7	0.7 ±17.8	1.0 ±17.5	*0.35*
BC worry (CWS: 8-32)	14.7 ±3.8	15.5 ±3.9	14.7 ±3.6	15.6 ±3.8	0.2 ±3.2	-0.0 ±3.8	*0.08*
Risk (0-100) perception: hereditary BC	41.1 ±24.3	43.0 ±21.3	33.7 ±30.5	35.6 ±26.2	-6.6 ±30.8	-7.9 ±23.0	*0.46*
Risk (0-100) perception: 2nd BC	43.3 ±28.1	49.5 ±26.8	39.6 ±26.2	48.1 ±25.8	-4.2 ±24.6	0.4 ±27.1	*0.15*

* Reported P-values for T1-To values are associated with the main effect for choice of procedure (DNA-direct versus DNA-intake) in repeated measurements ANOVA, corrected for baseline differences (see Table 1) as covariates. No main effects for time or interaction effects between time and choice of procedure was found.

Reasons for choice of procedure

Self-reported reasons for choosing DNA-direct were (multiple reasons per participant possible, not cumulative): the hope for faster *BRCA*-results (36%), no travel time (26%), received information was sufficient (20%), no extra hospital visit e.g. on top of ongoing chemo/radiotherapy (18%), already had ample information (16%), ease of reading information at home (16%) and choice of BC therapy depending on *BRCA*-status (2%). Self-reported reasons for DNA-intake were personal contact (71%), asking questions (29%) and bringing family (5%).

Processing times and *BRCA*-mutation detection rate

Median processing time (triage call to patient *BRCA*-result disclosure) was lower at 70 [23–280] days for DNA-direct versus 103 [22–303] days for DNA-intake (p=0.002). Median testing time (start *BRCA*-mutation testing to counselor receiving *BRCA*-result) was 34 [7–64] days and did not differ between procedures. *BRCA*-mutation detection rate was equal at 8%; however, of those tested, 65% (n=62/95) of DNA-direct participants and 74% (n=37/50) of DNA-intake participants fulfilled international guideline selection criteria (p=0.35). Two DNA-intake participants decided to wait (one on counselor's advice) despite fulfilling criteria; another participant's mother was the preferred relative for testing. The remainder did not fulfill criteria and were reassured by genetic counseling that *BRCA*-mutation testing was not necessary. If criteria were strictly enforced in DNA-intake, the mutation detection rate of 11% would still not differ from 8% in DNA-direct (p=0.74). Following negative *BRCA*-results and genetic counseling, 2 DNA-direct and 1 DNA-intake participants were tested for Cowden syndrome (*PTEN*), 1 in DNA-direct for familial melanoma (*FAMMM*). 1 DNA-intake participant did not fit *BRCA*-criteria, but was tested for hereditary stomach cancer (*CDH1*). Mutations in other genes than *BRCA1/2* were not detected.

Family relations and communication

92% of participants spoke to their nuclear family multiple times per week, with excellent relationship quality (median 9 [5–10] on scale 1–10). Family of origin showed good quality (8 [1–10]) with 43% speaking multiple times per week and 45% weekly to several times a month. Family communication (ODHCF) was excellent (median 5 [2–5] on scale 1–5). No differences were found in DNA-direct versus DNA-intake.

Interviews

One DNA-intake *BRCA*-mutation carrier declined, resulting in a total of 29 interviews (questions in Table 3): 17 DNA-direct and 12 DNA-intake participants. The main additional finding was that not all DNA-direct information formats had been used. Almost all (16 of 17) DNA-direct interviewees had read the informational letter, but one preferred the

Table 3: Semi-structured questions used for the follow-up telephone interview.

What did you think of the information that was sent home / discussed during intake?
Which information (sources) about genetic testing did you use?
What would you normally do if you are worried about your health?
When and for what reason did you decide to start the genetic blood test?
What did you think of the choice: an intake consultation vs. information sent home?
How did the consultation(s) with the genetic counselor go?
Did you speak to any other professionals about the results? (e.g. social worker)
What would you advise another person in the same situation to do?
Are you satisfied with the overall process of genetic counseling and testing?

digital formats. Overall, these had been used less: in total, 6 visited the website and 4 saw the movie. All interviewed participants in both groups were satisfied with information prior to *BRCA*-mutation testing and the overall process.

DISCUSSION

More patients with BC chose the new format of *BRCA*-mutation testing without prior face-to-face genetic counseling (DNA-direct) over the current standard (DNA-intake). Our hypothesis that psychological distress would not be increased by DNA-direct was proven by lower scores than DNA-intake in both general distress (GHQ-12) and heredity-specific distress (IES) at baseline and at follow-up. This suggests patients with higher distress were more likely to opt for initial face-to-face contact prior to genetic testing and remained more distressed at follow-up. DNA-direct participants were highly satisfied. At this moment, we do consider the new DNA-direct procedure to be preferred by and appropriate for the majority of BC patients especially those without pre-existing psychological problems similar to DNA-direct participants in our study. Further implementation does require continued evaluation of patient experiences, considering the (expected) low number of *BRCA*-mutation carriers identified using DNA-direct in this study. However, current study results are promising for the overall group. Some DNA-direct participants reacted especially positive as they were still in BC treatment. In this period, an extra hospital visit was considered a burden while reading information at home and drawing blood during chemo/radiotherapy sessions, made genetic testing accessible. Similarly, DNA-direct participants were more likely to have children living at home, possibly leading to more time constraints. Other reasons included the ease of (re)reading the written and digital information at their own convenience. Face-to-face genetic counseling by a certified genetics professional remained important also in the DNA-direct procedure. Our study provides evidence that receiving such counseling after

availability of *BRCA*-mutation testing results is acceptable. Personalized information about familial cancer risks and surveillance options could thus immediately be provided at first face-to-face contact with a trained genetic counselor, with one month shorter processing time than in DNA-intake. This was achieved without preferential treatment by our laboratories as reflected by equal testing time.

Written materials are used by 30% of cancer patients for cancer information, the internet by 36% of BC patients.[144] Using these patient preferred formats allowed rereading information to improve patient recall. Accurate information was ensured by directing patients to our own materials, followed by face-to-face genetic counseling at *BRCA*-result disclosure; until then telephone/e-mail contact was available for personal questions. DNA-direct participants were satisfied with the information sent home, although few made use of all different information formats offered: most had only read the written informational letter and all telephone/e-mail contact (n=14) concerned logistics. Offering a variety of information sources seems valuable because some preferred digital over written formats, others considered the availability of telephone/e-mail contact – even if unused – reassuring. Information redundancy across these different formats allowed patients to choose their own preferred format, yet still receive the same pre-test information.

Different information formats in genetic testing have been studied before. Jewish women in Canada approached by telephone and letter for *BRCA*-mutation testing showed no negative psychological impact.[145] Information about treatment-focused *BRCA*-mutation testing to BC patients in written or consultation form seemed equally effective in an ongoing Australian study.[146] Given the choice to receive results by consultation or letter, most patients tested presymptomatically for *BRCA* or Lynch syndrome in another Dutch study chose disclosure by letter, without excess distress and increasing efficiency.[147] Initial genetic counseling by telephone was equal to in-person contact in a Swedish randomized study, showing high patient satisfaction rates.[148]

More DNA-direct participants reported strong (rather than moderate) satisfaction with their choice to start *BRCA*-mutation testing, compared to DNA-intake. Surprisingly, fewer DNA-direct than DNA-intake participants would start *BRCA*-mutation testing again. Participants may have misinterpreted the question to start *BRCA*-mutation testing if given a second chance, as doing such testing while the majority already knew they were not a *BRCA*-mutation carrier, thus not necessarily reflecting satisfaction. Also, fewer DNA-direct participants would recommend *BRCA*-mutation testing to another BC patient, but those indicating why showed reluctance to influence another individual's choice, rather than (non-)satisfaction.

Non-randomization limits the generalizability of our study. We chose not to randomize to determine BC patient preferences and arguments for or against DNA-direct. When all BC patients would have preferred a face-to-face intake consultation, our conclusion would have been different. However, a majority of BC patients did choose DNA-direct, proving otherwise. This approach did lead to significant baseline differences between the DNA-direct and DNA-intake groups. For example, DNA-intake participants showed higher distress than DNA-direct. As no interaction or time effect was demonstrated, patients with higher distress seemed to prefer initial face-to-face contact prior to *BRCA*-mutation testing and remained more distressed at follow-up compared to DNA-direct participants. Educational level was also lower in DNA-intake, previously established as an important confounder when providing *BRCA*-mutation testing services.[149] To limit effects on study results, statistical correction for these baseline differences was performed. However, DNA-direct may be a best fit for those patients who match the overall profile of DNA-direct participants in our study: higher educated and better informed patients, who are more certain of genetic testing and show less distress.

Selection bias may have influenced our results: those with current psychological problems were excluded, as they may be prone to higher distress after *BRCA*-mutation testing. Patients did not experience difficulty with family communication as a barrier to DNA-direct, although counselors should remain vigilant for such problems. Another limitation is that effects on processing time are health system dependent and may provide different results elsewhere.

BRCA-mutation detection rate was equal in both groups with all detected *BRCA*-mutation carriers fulfilling guideline criteria for *BRCA*-mutation testing. We conclude that raising efficiency by selecting eligible BC patients on referral for genetic testing by other medical specialists, and reducing the number of face-to-face consultations (higher costs compared to telephone contact) and processing time while increasing patient participation and providing to-the-point counseling, weighs up against some patients being tested without fulfilling guideline criteria for *BRCA*-mutation testing (35%). This does underline the importance of improving physician knowledge of appropriate referral criteria.[38]

In conclusion, more BC patients preferred replacing a face-to-face consultation with a trained genetic counselor prior to *BRCA*-mutation testing by telephone, written and digital information, the majority being strongly to moderately satisfied with the procedure followed, without increased distress as compared to the face-to-face intake procedure.

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Conflict of interest statement

The authors declare no conflict of interest.

Chapter 5

High satisfaction and low distress in breast cancer patients one year after *BRCA*-mutation testing without prior face-to-face genetic counseling

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ABSTRACT

According to current practice most breast cancer (BC) patients receive face-to-face genetic counseling prior to *BRCA*-mutation testing (DNA-intake). We evaluated a novel format by prospective study: replacing the intake consultation with telephone, written and digital information sent home. Face-to-face counseling then followed *BRCA*-mutation testing (DNA-direct). From August 2011 to February 2012, 161 eligible BC patients chose either DNA-direct (intervention: 59%) or DNA-intake (control: 41%). One year after *BRCA*-result disclosure, 108 participants (59 DNA-direct: 55%) returned long-term follow-up questionnaires. Questionnaires included satisfaction and psychological distress. All participants were satisfied and 85% of DNA-direct participants would choose this procedure again; 10% would prefer DNA-intake and 5% were undecided. In repeated measurements ANOVA, general distress (GHQ-12, p=0.01) and BC-specific distress (IES-bc, p=0.03) were lower in DNA-direct than DNA-intake at all time measurements. Heredity-specific distress (IES-her) did not differ significantly between groups. Multivariate regression analyses showed that choice of procedure did not significantly contribute to either general or heredity-specific distress. BC-specific distress did contribute to both general and heredity-specific distress. This suggests that higher distress scores reflected BC experience, rather than the type of genetic diagnostic procedure. In conclusion, the large majority of BC patients that used DNA-direct reported high satisfaction without increased distress both in the short-term, and one year after conclusion of genetic testing.

Keywords

BRCA – breast cancer – counseling – DNA – genetic – hereditary

INTRODUCTION

Patients confronted with a diagnosis of breast cancer (BC) desire quick answers about their personal situation in light of their risk of a hereditary predisposition.[119] Should a pathogenic *BRCA1/2*-mutation be found, BC patients are at an increased risk of up to 60% of a second primary BC[31-33] which may influence the choice of BC treatment.[96] For the additional high risk for ovarian cancer (20-60% for *BRCA1* and 2-20% for *BRCA2*[31-33]) prophylactic surgery is recommended.[64] Family cascade screening may identify unaffected *BRCA1/2*-mutation carriers with an increased lifetime risk of 40-80% for BC.[31-33] *BRCA1/2*-mutation carriers are eligible for yearly BC screening or prophylactic surgery from 25 years of age.[10] Current genetic counseling practice typically involves a face-to-face counseling session with a genetic counselor prior to diagnostic *BRCA*-testing.[150] This may add several weeks to the period of diagnostic uncertainty regarding *BRCA1/2* gene status. We reasoned that a shorter trajectory of genetic information provision might be advantageous for BC patients with concerns about their risk of a hereditary predisposition.

To achieve this, we previously evaluated short-term patient experiences with a novel format replacing the initial face-to-face consultation prior to *BRCA*-mutation testing (usual care, DNA-intake procedure) by telephone, written and digital information with a blood drawing kit sent to their home address (DNA-direct procedure).[143,151] In both procedures, *BRCA*-results were disclosed in face-to-face consultations by an experienced genetic counselor, including personalized counseling and cancer prevention recommendations for both patients and their families.[143] Given a free choice between these procedures, 59% (95 of 161) of eligible BC patients (p=0.03) chose the new format of *BRCA*-mutation testing without prior face-to-face genetic counseling (DNA-direct), proving an interest in this new procedure. Several weeks (median 5 [2–22]) after *BRCA*-result disclosure, DNA-direct participants were highly satisfied and showed lower psychological distress than DNA-intake, suggesting that patients with higher distress were more likely to opt for initial face-to-face contact prior to genetic testing and remained more distressed throughout the procedure.[151]

While these short-term results were reassuring, literature shows different trajectories of change in psychological adjustment after BC diagnosis: while the majority remains even or stabilizes one year post-diagnosis, a small group deteriorates.[152] This trend was shown in older (>65 years) BC patients, where diminished social support was predictive of deteriorating quality of life.[153] BC patients may also be vulnerable due to family cancer history, e.g. deaths of family members diminishing their social support systems. Family history is often the reason for referral to genetic services[154], but adding a genetic

diagnostic procedure could influence long-term psychological adjustment. We therefore sought to determine long-term effects and acceptability of the novel DNA-direct procedure, in order to assess whether distress is triggered at a later time.

This study thus compared long-term experiences of BC patients (satisfaction and psychological distress) between the novel DNA-direct procedure and usual care (DNA-intake), measured one year after *BRCA*-result disclosure. We hypothesized that patient satisfaction in both procedures would remain stable over time (as we observed previously shortly after *BRCA*-result disclosure), and that DNA-direct does not induce increased distress in short- or long-term.

METHODS

Participants

The study protocol was previously published.[143] In short, following approval by the local medical ethics committee, all female patients (previously) diagnosed with BC and referred to the department of Human Genetics at Radboudumc between August 2011 and February 2012 were eligible (Figure 1). Exclusion criteria were psychological problems requiring treatment, difficulty with Dutch text, or known *BRCA*-families. To evaluate whether there was a preference for DNA-direct, BC patients were free to choose between procedures.

Study procedure

Previous results were published[151] based on 161 responses on baseline (T0) questionnaires. Of these, 95 (59%) chose the DNA-direct procedure over DNA-intake, and 146 (n=87 DNA-direct) returned short-term follow-up (T1) questionnaires sent two weeks after *BRCA*-result disclosure. Mutation detection rate was equal at 8% in both groups; processing time was one month shorter in the DNA-direct procedure. Additional long-term follow-up (T2) data are presented here, collected from questionnaires sent one year after *BRCA*-result disclosure to previous T1 responders; participation was voluntary.

DNA-direct procedure

In the novel DNA-direct procedure, patients received telephone (triage call by a trained medical doctor), written and digital information (website, educational movie) at home. The triage call (median 9 [5–20] minutes) served to check exclusion criteria primarily meant for pre-test psychosocial assessment of difficulty with Dutch text, psychological problems or family communication problems (Figure 1). Non-excluded patients were all offered the choice of DNA-direct versus DNA-intake, without genetic counseling.

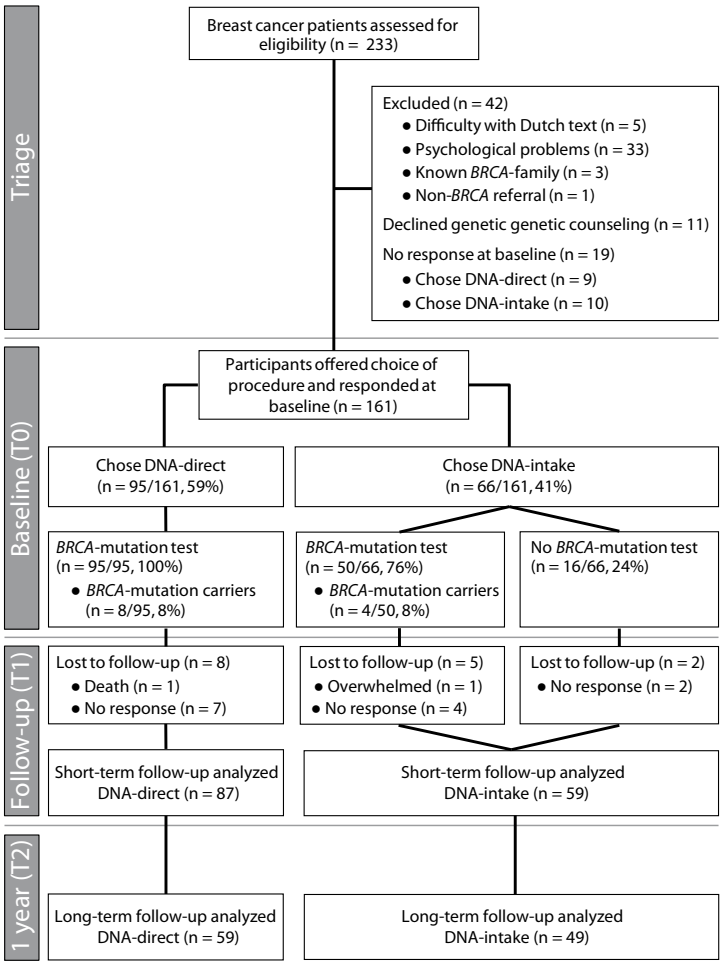

Figure 1: Flowchart of patient inclusion, short term and one year follow-up, procedure proportions and *BRCA*-results.

Patients choosing DNA-direct received an informational letter and website with video covering basic information about BC, heredity and genetic testing, similar to a pre-test consultation. A blood drawing kit was included to start *BRCA*-mutation testing. Written informed consent for DNA-direct and family history forms were required before diagnostic testing was initiated. Telephone or e-mail contact with the physician researcher (AS) was available (used by 14 participants, only regarding logistics). *BRCA*-results were disclosed in a face-to-face consultation of 45 minutes (equal to the pre-test DNA-intake consultation) by one of five experienced genetic counselors. Further details were previously published.[143,151]

Instrumentation

Full psychometric details of standardized measures were previously published.[143] At 1 year follow-up (T2), the primary study outcomes were: satisfaction regarding choice of procedure (T1/T2), general distress (T0/T1/T2: GHQ-12[129] scale 0–12, Cronbach's α in this study=0.84 at T0 / 0.89 at T1 / 0.88 at T2) and heredity-specific psychological distress (T0/T1/T2: IES-her[132,133] scale 0–75, α=0.93 / 0.94 / 0.95).

Secondary psychological measures were BC-specific distress (T0/T2: IES-bc[132,133] α=0.93 / 0.92), global quality of life (T0/T1/T2: selected from EORTC-QLQ-Q30[127] scale 0–100, α=0.85 / 0.84 / 0.91), BC worry (T0/T1/T2: CWS[135] scale 8–32, α=0.84 / 0.85 / 0.82), risk perception of hereditary BC and 2nd BC (T0/T1/T2: visual scales 0–100). Other secondary T2 outcomes were: coping style (shortened TMSI[16,155]) categorizing responders as more monitoring (subscale α=0.69) i.e. actively seeking information about medical threats, more blunting (subscale α=0.69) i.e. seeking distraction, or neutral, as used in a previous study[156]; and open-ended questions regarding a) perceived causes of their BC and b) most important aspects for other patients to know about genetic testing (>10% reported).

Baseline differences

In previous analyses[151], significant differences in baseline (T0) sociodemographic and BC characteristics were found between DNA-direct and DNA-intake groups (Table 1). Most importantly, DNA-direct participants reported higher website use (p=0.01), more prior information by their referring physician about personal consequences (p=0.004), less prior information by their referring physician about genetics in general (p=0.008) and lower decisional conflict i.e. difficulty making a decision whether to start DNA-testing (p=0.01). Baseline differences were corrected for statistically as described below.

Data analysis

Data is presented using descriptive statistics. To compare DNA-direct versus DNA-intake for each T2 outcome, the unpaired t-test was used for continuous, Mann-Whitney U test for ordinal and chi-square/Fisher's Exact test for nominal/dichotomous variables. Eight baseline differences (Table 1) were included as covariates in repeated measurements ANOVA used to test for changes over the three time measurements (T0, T1, T2) between DNA-direct versus DNA-intake (group) in psychological outcomes (general distress, heredity-specific distress, BC-specific distress, quality of life, BC worry and risk perception of hereditary BC and 2nd BC) and multivariate regression analyses of non-psychological outcomes showing univariate differences. Correlations between distress (T2: general, heredity-specific, BC-specific) and choice of procedure (DNA-direct or DNA-intake), sociodemographic characteristics (T0: age at inclusion, educational level), BC

Table 1: Relevant baseline differences (p<0.05) in sociodemographic and breast cancer (BC) characteristics for all BC patients choosing DNA-direct (novel format) or DNA-intake (usual care) as evaluated in previous analyses.[151]

Characteristic	DNA-direct n=95: N (%) or median [range] or mean±SD	DNA-intake n=66: N (%) or median [range] or mean±SD	P
Age at inclusion	49 [23-73]	53 [28-74]	*0.10*
Age at 1st BC diagnosis	47 [23-71]	49 [28-74]	*0.15*
Months since last BC	6 [0-247]	6 [0-195]	*0.92*
***BRCA* referral criteria**			
- positive family history	75 (79%)	53 (80%)	*1.00*
- age at BC <40yrs	29 (31%)	13 (20%)	*0.15*
- ovarian cancer in patient	4 (4%)	2 (3%)	*1.00*
Family characteristics			
- mother with BC	17 (18%)	13 (20%)	*0.84*
- sister with BC	17 (18%)	15 (23%)	*0.55*
- age (yrs) youngest with BC	40 [23-62]	42 [26-64]	*0.03* *
- children living at home	55 (58%)	26 (39%)	*0.03* *
Educational level			*0.01* *
- high	39 (41%)	13 (20%)	
- medium	27 (28%)	25 (38%)	
- low	29 (31%)	28 (42%)	
Use of BC websites	50 (53%)	21 (32%)	*0.01* *
Information provided by referring physician			
- genetics in general	25 (26%)	31 (47%)	*0.008* *
- personal consequences	39 (41%)	13 (20%)	*0.006* *
- outcomes of genetic testing	32 (34%)	12 (18%)	*0.03* *
Decisional conflict (DCS: 0-100)	*n=87:* 16.2±13.9	*n=58:* 23.2±10.8	*0.001* *

* Statistically significant p<0.05: baseline differences included as covariate in multivariate analyses.

characteristics (To: age at 1st BC diagnosis, months since last BC, *BRCA* referral criteria, family characteristics) and psychological variables (T2: quality of life, coping style, BC worry, risk perception for heredity and for second BC) were assessed using Pearson's correlation coefficients. Characteristics with significant correlations were used as independent variables in multiple backward linear regression analysis for the determinants of each psychological distress measure. The probability level for statistical significance testing was set at 0.05 (two-tailed). The SPSS 20.0 statistical package was used to analyze the data.

Genetic counselors' experiences

Previously unreported, the five involved genetic counselors filled in a yes/no checklist after each individual DNA-direct consultation to determine whether they experienced: 1) good contact with the patient, 2) unexpected patient reactions, 3) need for a follow-

up consultation, 4) need for non-standard psychosocial support, 5) the patient having made an informed choice to start *BRCA*-testing, and 6) the retrospective preference for a pre-test intake consultation. They were also asked for their general opinions during a joint DNA-direct counselor meeting.

RESULTS

A total of 108 BC patients returned one year follow-up (T2) surveys of whom 59 had previously chosen DNA-direct (55%), five of which were identified as *BRCA*-mutation carriers, versus 49 participants who had chosen DNA-intake of which one was a *BRCA*-mutation carrier.

Satisfaction with choice of procedure

All participants in both groups were satisfied with their choice of procedure, 75% strongly so; none reported regret. Most DNA-direct participants (85%) would choose this procedure again (1 emphasized the benefit of taking action from home during BC diagnosis/treatment) whereas 10% now preferred DNA-intake (1 stated this seemed more personal) and 5% did not know (1 clarified dependency on their health at that time). In DNA-intake, most (80%) would choose this procedure again with 10% emphasizing personal contact, but 16% now preferred DNA-direct (none clarified) and 4% did not know (depending on explanation of the procedure).

Two-thirds (63%) of DNA-direct versus one-third (31%, p=0.001) of DNA-intake reported that their recommended procedure to another patient would depend on that individual person: their preferences for personal contact, information formats, comfort using digital media, questions and worries, capability of processing information, prior medical knowledge, social support. DNA-direct was specifically recommended by 24% of DNA-direct and 10% of DNA-intake participants (1 felt the choice could also be made using DNA-direct, 1 would recommend DNA-intake instead if the person had many worries). DNA-intake was recommended by 9% of DNA-direct (1 mentioned the ability to ask questions) and 57% of DNA-intake (1 emphasized their own preference for face-to-face contact). 5% of DNA-direct and 2% of DNA-intake participants were uncertain which procedure to recommend; all stated it was a personal choice.

Psychological distress

As shown in Table 2, no main effects for time (within subjects) were found for any psychological distress measure. In DNA-direct, lower scores were reported for general distress than DNA-intake (GHQ-12: p=0.01, between subjects). Notably, a near-significant

Table 2: Psychological measures for all breast cancer (BC) patients choosing DNA-direct (novel format, n=59) or DNA-intake (usual care, n=49) responding at follow-up one year post *BRCA*-result disclosure (T2). Estimated means±standard deviations are reported following correction for baseline differences (see Table 1) in repeated measurements ANOVA.

Characteristic	T0		T1		T2		
	DNA-direct n=59	DNA-intake n=49	DNA-direct n=59	DNA-intake n=49	DNA-direct n=59	DNA-intake n=49	P*
General distress (GHQ-12: 0-12)	2.7±3.0	4.2±3.5	1.9±3.0	3.9±3.5	1.8±3.0	2.1±3.5	**0.01** **
Heredity-specific distress (IES-her: 0-75)	13.9±14.5	15.1±14.9	12.3±16.0	14.9±16.2	9.1±12.9	13.4±13.0	*0.26*
BC-specific distress (IES-bc: 0-75)	17.0±15.7	23.7±15.8	*not measured*	*not measured*	12.4±14.2	18.1±14.4	**0.03**
Quality of Life (QoL: 0-100)	73.1 ±20.0	71.9±20.1	75.0±16.9	73.5±17.3	77.9±19.2	77.7±19.4	*0.76*
BC worry (CWS: 8-32)	14.1±3.8	15.2±4.0	14.5±3.0	15.2±3.3	13.5±3.8	14.8±3.3	*0.10*
Risk (0-100) perception: hereditary BC	40.4±24.7	41.1±25.2	32.8±29.9	32.4±30.5	38.6±29.2	38.7±29.8	*0.98*
Risk (0-100) perception: 2nd BC	45.4±29.2	44.1±29.5	37.7±24.7	41.8±24.9	38.9±28.4	43.2±28.9	*0.62*

* Reported P-values are associated with the main effect for choice of procedure (DNA-direct versus DNA-intake) in repeated measurements ANOVA: bold indicates statistical significance p<0.05. No main effects for time (within subjects) were found.

** Trend for interaction effect between time and choice of procedure: p=0.051. No other variables showed (trends for) interaction effects.

interaction effect between time and choice of procedure was found (p=0.051): as seen in Figure 2a, the difference in general distress between procedures appears greater at To and T1 than at T2. Corrected mean general distress scores for DNA-intake crossed the threshold for clinical relevance of GHQ-12≥4 at baseline (Figure 2a) but dropped below this threshold after *BRCA*-result disclosure; no clinically relevant distress scores were shown in DNA-direct. Heredity-specific distress (IES-her) did not differ significantly between procedures, nor showed an interaction effect. BC-specific distress in DNA-direct did score lower than DNA-intake (IES-bc: p=0.03) without an interaction effect. All heredity-specific and BC-specific distress scores remained below the clinical relevance threshold of IES≤26.

Variables significantly correlating with general distress (GHQ-12), heredity-specific distress (IES-her) or BC-specific distress (IES-bc) are shown in Table 3. Choice of procedure (DNA-direct versus DNA-intake) only correlated to heredity-specific distress, but was no longer significant following multivariate regression analysis. Higher BC-specific distress was a significant contributor to both general distress (p=0.01) and heredity-specific dis-

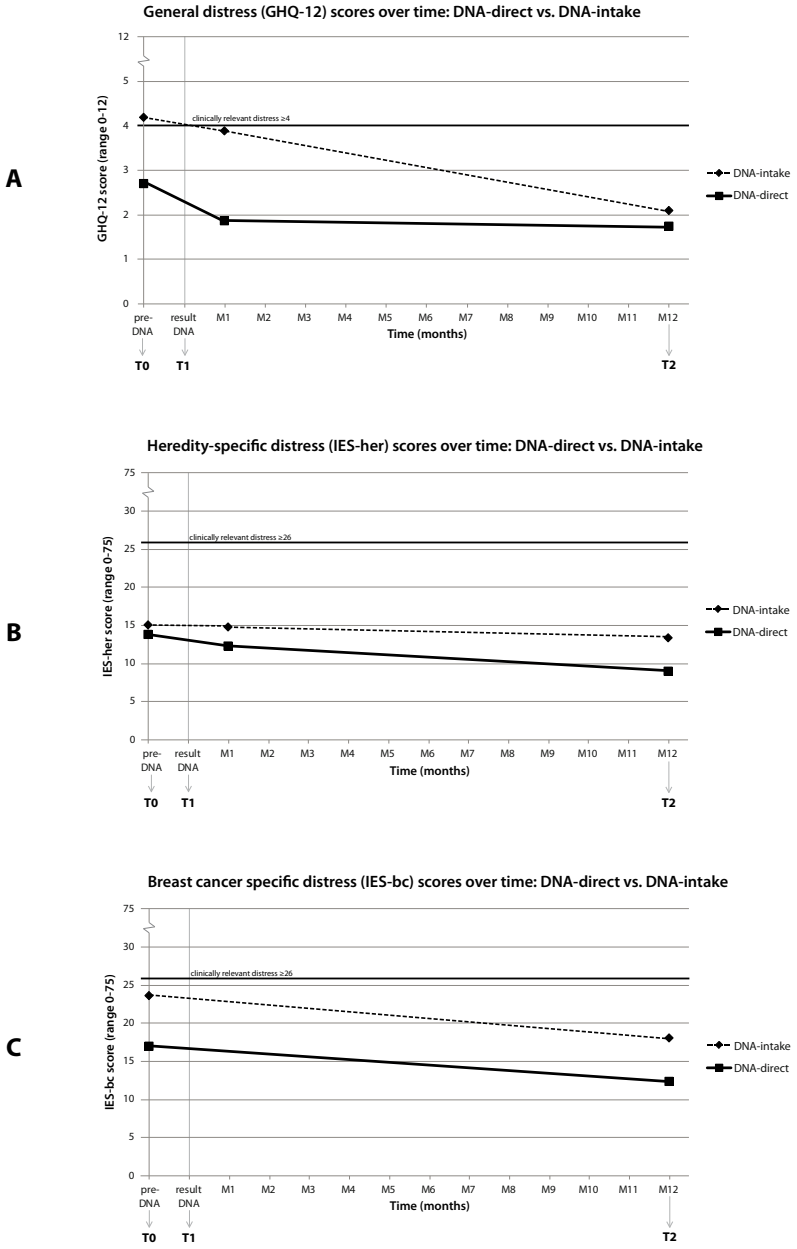

Figure 2: Changes over time in psychological distress measures: a) general distress (GHQ-12), b) heredity-specific distress (IES-her), and c) BC-specific distress (IES-bc). Significant group effects were found only in general distress (a) and BC-specific distress (c) without significant time effects in any measure.

Table 3: Determinants of psychological distress measures amongst all participating breast cancer (BC) patients choosing either DNA-direct (intervention) or DNA-intake (control), following correlation testing with choice of procedure, sociodemographics, BC characteristics and other psychological variables (significant correlations with p<0.05 shown).

Characteristic	Pearson's correlation coefficient	Multivariate regression analysis		
		P	Beta	95% confidence interval
General distress (GHQ-12)				
- Quality of Life (QoL)	-0.562	<0.001	-0.544	[-0.114 – -0.063]
- BC-specific distress (IES-bc)	0.255	0.011	0.205	[0.010 – 0.073]
- BC worry (CWS)	0.275	n.s.	-	-
- mother with BC	-0.363	n.s.	-	-
- age youngest relative with BC	-0.428	n.s.	-	-
- children living at home	0.196	n.s.	-	-
Heredity-specific distress (IES-her)				
- DNA-direct vs. DNA-intake	-0.192	n.s.	-	-
- BC-specific distress (IES-bc)	0.545	<0.001	0.386	[0.190 – 0.600]
- BC worry (CWS)	0.520	0.013	0.257	[0.239 – 1.983]
- sister with BC	0.206	0.022	0.183	[0.929 – 11.723]
BC-specific distress (IES-bc)				
- General distress (GHQ-12)	0.255	n.s.	-	-
- Heredity-specific distress (IES-her)	0.545	<0.001	0.304	[0.135 – 0.458]
- BC worry (CWS)	0.631	<0.001	0.452	[1.210 – 2.618]
- age at inclusion (years)	-0.233	0.024	-0.165	[-0.411 – -0.030]

tress (p<0.001). General distress was also more likely in participants with lower quality of life (p<0.001), while higher heredity-specific distress was associated with more BC worry (p=0.01) or having a sister with BC (p=0.02). More BC-specific distress was seen in those with higher heredity-specific distress (p<0.001), higher BC worry (p<0.001) or younger age at inclusion (p=0.02).

Secondary psychological outcomes

Quality of life, BC worry, risk perception for hereditary BC and 2nd BC (Table 2) did not differ between DNA-direct versus DNA-intake (between subjects) or over time (within subjects).

Perceived causes of breast cancer

As multiple reasons were possible per responder, percentages are not cumulative: heredity (30%), bad luck (30%), stress (14%) and hormonal factors e.g. oral contraception (14%) were reported as perceived causes of BC; 18% did not know. Only one significant difference was found: those in the DNA-direct group were more likely to perceive hered-

ity (e.g. "it runs in the family") as the cause of their BC than in DNA-intake (46% vs. 10%, p<0.001).

Important aspects of genetic testing

Responders felt (not cumulative) that other persons should know about: certainty and/or clarity about a hereditary predisposition (22%), consequences for family (18%), procedural aspects (18%), consequences of genetic testing (18%), early prevention (12%) and no full guarantees from test results (11%). No differences between DNA-direct and DNA-intake were found.

Genetic counselors' experiences

In a total of 88 reported DNA-direct disclosure sessions, genetic counselors achieved good contact with patients (94%), experienced few unexpected patient reactions (7%), few patients needing follow-up consultations (9%) or non-standard psychosocial support (2%), believed most patients made an informed choice to start *BRCA*-testing (76%) and in retrospect, did not prefer a pre-test intake consultation for the majority of patients (85%). In general, counselors reported the benefit of to-the-point and personalized counseling, saving time within the 45 minutes of a first face-to-face consultation to discuss personal consequences of the known *BRCA*-result for the patient and her family.

DISCUSSION

The current evaluation continues our previous study, which had already shown that more patients with BC chose the new format of *BRCA*-mutation testing without prior face-to-face genetic counseling (DNA-direct) over the current standard of face-to-face counseling both prior to and following *BRCA*-mutation testing (DNA-intake). Follow-up of these patients showed that there was no increase in psychological distress at either short- or long-term; in fact, the DNA-direct participants scored lower on both general and BC-specific distress than DNA-intake. We conclude from these study results that the DNA-direct procedure i.e. face-to-face counseling after availability of *BRCA*-mutation testing results, is appropriate for the majority of BC patients, in particular those similar to DNA-direct participants in our study. Patients without pre-existing psychological problems may prefer to arrange *BRCA*-mutation testing from home due to reasons associated with their BC diagnosis and treatment, information needs and preferences, as well as certain family characteristics (e.g. children living at home). In retrospect genetic counselors did not prefer DNA-intake for most patients (85%). Counselors emphasized to-the-point and personalized counseling with more time to discuss personal conse-

quences rather than general *BRCA* information: most patients did not require additional follow-up (91%).

One interesting difference at long-term follow-up should be noted: more DNA-direct participants reported their belief that heredity (may have) caused their BC, but this was not reflected in reports of risk perception for hereditary BC, which remained equal between groups and over time. However, one of the baseline differences found between groups was that amongst DNA-direct participants, BC was diagnosed in their family at a younger age. Although no other clinical variables were previously found to predict for the choice of DNA-direct[151] this may suggest that these participants are more aware that their BC risk may still be moderately increased by familial factors, beyond *BRCA*-mutations. Risk perceptions for hereditary BC not changing over time for either group is also notable and in concordance with earlier literature showing that traditional genetic counseling and testing has no lasting effects on risk perception.[12,113] Improving patient risk perceptions remains a challenge for genetic counseling as a whole, but is not enhanced nor deteriorated due to the DNA-direct procedure.

Study limitations

As described previously[151], non-randomization of our study participants limits the generalizability of our study results. DNA-direct may therefore be most appropriate for those BC patients matching the overall profile of DNA-direct participants in our study: those who are higher educated and better informed, as well as comfortable with or even preferring different information formats beyond face-to-face contact. We now consider randomization unethical, as our study result suggest a link between distress and self-selection. Another study limitation is the low number of *BRCA*-positive results which may have influenced our study results, as these patients are the most likely to experience distress after disclosure.[154] However, this low number is reflective of standard clinical genetic practice therefore does not affect generalizability of our study results.

No formal cost-effectiveness analyses have been performed, but DNA-direct reduced face-to-face consultation time for both genetic counselors and the surrounding resources at the outpatient clinic. The DNA-intake procedure included a pre-test session of 45 minutes and a post-test session of 15 minutes (total 60 minutes). The DNA-direct procedure only included a post-test session of 45 minutes. However higher uptake of *BRCA*-testing (100% in DNA-direct versus 76% in DNA-intake) might suggest more patients were *BRCA*-tested unnecessarily in DNA-direct: *BRCA*-testing was only indicated if one or more of familial risk scores (e.g. FHAT[123], Myriad[124], Claus/van Asperen[126]) exceeded certain thresholds. But familial risk selection criteria for *BRCA*-testing were not fulfilled by some patients *BRCA*-tested in both groups: 35% in DNA-direct versus

26% in DNA-intake. Mutation detection rate remained equal in both groups. This reflects that the choice of procedure did not result in different numbers of patients *BRCA*-tested, whereas offering DNA-direct alongside DNA-intake increased patient participation and reduced processing time. We consider this to be the greatest benefit of the DNA-direct procedure, despite cost-effectiveness not being proven, dependent on additional *BRCA*-test costs.

Practice implications

Participants who chose the traditional DNA-intake procedure reported higher general and BC-specific distress, even one year after *BRCA*-result disclosure. This supports our earlier notion[151] that distressed patients were more likely to choose face-to-face counseling prior to genetic testing. However, choice of procedure did not appear to be a significant contributor to general and heredity-specific distress, instead both were associated with BC-specific distress. This further suggests that higher distress scores were based on the experience of BC, not the (chosen) genetic diagnostic procedure; and that those who feel more distressed and may be in need of prior psychosocial support, self-selected to the DNA-intake procedure where such support was immediately available. Offering DNA-direct as an alternative to the standard DNA-intake, to match individual preferences for information formats prior to *BRCA*-mutation testing, therefore is considered acceptable in the light of our follow-up results. This adds to an ever-growing body of literature[147,157-160] showing that these new models of cancer genetic services varying in combinations of face-to-face, telephone and/or digital communication, pre- and/or post *BRCA*-testing, are acceptable.[5] Positive patient experiences with newer multi-gene panels[161] have currently only been proven after pre-test counseling regarding possible unsolicited or unclear findings.[162] Therefore we do not currently recommend DNA-direct for multi-gene panels.

Research recommendations

Other target groups for DNA-direct may be evaluated. For example, *BRCA*-mutations account for 5-16% of all ovarian cancer cases[163] and guidelines now recommend referral of all patients with ovarian cancer regardless of age or family history.[36] Patients with ovarian cancer strongly supported genetic testing around the time of diagnosis[164] and may be excellent candidates for DNA-direct in the future. Further research may also focus on alternative service models for the multi-gene panel setting, starting with those now used for conventional single-gene testing.[5]

Conclusions

BC patients who had chosen to forego personal genetic counseling prior to *BRCA*-mutation testing, and instead receive a combination of telephone, written and digital

information reported high satisfaction and low distress both several weeks and one year after *BRCA*-result disclosure. Distress is triggered by the BC diagnosis, not genetic testing. The novel DNA-direct procedure appears acceptable for BC patients alongside the traditional face-to-face intake procedure.

ACKNOWLEDGEMENTS

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Conflict of interest

Aisha S. Sie, Liesbeth Spruijt, Wendy A.G. van Zelst-Stams, Arjen R. Mensenkamp, Marjolijn J.L. Ligtenberg, Han G. Brunner, Judith B. Prins and Nicoline Hoogerbrugge declare that they have no conflict of interest.

Informed consent

All procedures followed were in accordance with the ethical standards of the local medical ethical board of the Radboud University Medical Center and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

STAGE II

Genetic testing and counseling

"The beginning of knowledge is the discovery of something we do not understand."

(Frank Herbert)

Chapter 6

Can we test for hereditary cancer at 18 years when we start surveillance at 25? Patient reported outcomes

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ABSTRACT

Background: DNA-testing for *BRCA1/2* or Lynch syndrome is possible from the age of 18 years, although surveillance usually starts at 25. Some patients regret their decision of testing before age 25. This retrospective study evaluates whether the testing age should be above 25 years to prevent adverse effects such as regret or decisional conflict, by determining the percentage and characteristics of patients reporting these problems.

Patients/Methods: 111 of 219 patients (51%) tested for *BRCA1/2* mutations or Lynch syndrome between 18-25 years from July 1996 to February 2011, returned self-report surveys. Primary measures were regret, decisional conflict and family influence. Secondary measures included quality of life (QoL), coping style, impact of genetic testing, and risk perception.

Results: Median age was 27 [21-40] years, with 86% female. 73% was tested for *BRCA1/2*, 27% for Lynch syndrome. Only 3% reported regret, however 39% had moderate (32%) to severe (7%) decisional conflict. Regression analysis revealed that decisional conflict was associated with more monitoring/neutral coping style ($p<0.03$) or paternal/no family mutation ($p<0.02$); there were no differences in QoL, impact or risk perception. 42% were mutation carriers, showing equal decisional conflict to non-carriers. 68% would recommend testing <25 years; 77% desired surveillance <25 years if a mutation carrier.

Conclusion: Almost no patient tested for hereditary cancer between 18-25 years regretted this decision. A third reported retrospective decisional conflict, especially those actively seeking information when faced with a threat and/or those with a paternal or unknown inheritance. These patients may benefit from decisional support and personalized information.

Keywords

young adult – hereditary – cancer – BRCA – Lynch syndrome – decision making

BACKGROUND

Following international guidelines[45], DNA-testing of the *BRCA1/2* genes for hereditary breast cancer, or the mismatch repair (MMR) genes for hereditary colon cancer (Lynch syndrome) is possible from the age of 18 years. However, surveillance for *BRCA1/2* or Lynch syndrome does not usually start until the age of 25 years (although prior to policy changes in 2008, surveillance for Lynch syndrome was advised from 20-25 years).[57,61] Thus, a younger carrier might be aware of their mutation status, but there is no indication to act on this knowledge (by surveillance or preventive surgery) until age 25.

In general, young adults between 18 and 25 years of age are in the midst of a vital, but hectic phase of life: they are expected to become fully independent adults, while still sensitive to family influences.[47,48] When faced with hereditary cancer, especially if a parent is involved, they may struggle with the need to break free from their family for their own self-development, versus family loyalty and involvement due to cancer. Their own cancer risk[165-167] and the experience of parental cancer in childhood or adolescence may lead to increased distress during genetic testing.[168] Specific support needs in young adults and distress due to the discrepancy between the desired age of testing versus current practice have previously been identified in another hereditary cancer syndrome, familial adenomatous polyposis (FAP).[49,50] As FAP is associated with a much earlier onset of symptoms, these studies cannot necessarily be generalized to *BRCA1/2* and Lynch syndrome, but do indicate the need for further study of this particular age group in these syndromes.

The question remains whether these young adults are able to anticipate all the short and long term consequences of their decision. Neurophysiologic research shows that the brain (especially the frontal lobes responsible for planning and execution) is still in active development until 25 years.[48,169] It is currently unclear what this means for the development of cognitive competencies such as future orientation[170], decision-making[171], self-identity and reflection.[172] However, these are important in genetic counseling as decisions must be based on expectations regarding possible future consequences of a yet unknown result.[172]

Young adults between 18 and 25 years of age may experience fewer benefits from genetic testing than older patients with a concrete goal to start prevention measures immediately. They may feel especially vulnerable due to the knowledge of higher cancer risks without clear clinical management guidelines until the age of 25.[66] In our hospital, some of these young adults thus indicated regret of their decision to start DNA-testing for *BRCA1/2* mutations or Lynch syndrome before the age of 25 years. Looking back, they

considered themselves incapable of making a decision of such importance at that time. This may refer to so-called decisional conflict. While regret concerns emotional remorse following a choice, decisional conflict is a state of uncertainty about a course of action due to feeling uninformed, unsupported or unclear about personal values.[138,139]

However, as other young adults had not reported such problems, age does not seem to be the only factor involved; psychological aspects such as risk perception may also be relevant. Some studies suggest that those with high perceived risk are more likely to start genetic testing.[173] Risk perception is related to many factors including family history, stress and coping style. The uptake of genetic testing was studied in relation to two coping styles, monitoring (actively seeking information when faced with a threat) and blunting (avoidance of information). Patients with a monitoring coping style did not have a higher uptake of genetic testing[174], but patients choosing not to undergo testing had higher anxiety levels than those who were tested, suggesting that coping through avoidance (blunting) resulted in lower uptake.[173] Monitoring recipients of indeterminate or positive results reported increased distress.[175] No differences were found in coping styles of patients tested for *BRCA1/2* mutations or Lynch syndrome[176], allowing pooled evaluation.

The aim of this retrospective study was to assess whether the testing age should be above 25 years in order to prevent adverse effects such as regret or decisional conflict, by determining the percentage and characteristics of patients reporting such problems in retrospect.

PATIENTS AND METHODS

Participants

All patients tested for mutations in either the *BRCA1/2* genes or mismatch repair (MMR) genes associated with Lynch syndrome between July 1st 1996 and February 14th 2011 in the Radboud University Nijmegen Medical Centre (RUNMC), who were younger than 25 years of age at the time of testing (n=290), were eligible for this study. Patients were initially excluded if they were younger than 18 years of age when tested (n=10) or if they had been counseled in another medical center (n=40). Medical files of the remaining 240 patients were reviewed for further reasons for exclusion: death (n=9), intellectual disability (n=5), expatriation (n=4), tumor but no gene testing (n=1), unknown address (n=2). A final total of 219 patients were included in the study.

Study procedure

Patients were invited by mail to fill in an online self-report survey within two weeks. If needed, a reminder letter with paper survey was sent a month later. Surveys were returned by 111/219 patients (51%). Despite checking addresses before mailing out surveys, 1 was returned as unknown resident.

Measures

Decision-making

Regret

Regret of the decision to start DNA-testing before 25 years was measured by a 4-point Likert-scale from 1 'not at all' to 4 'very much'. Patients indicated to start DNA-testing again if given a second chance now, by answering 'yes, at the same moment', 'yes, but at a later time' or 'no, not at all'.

Decisional conflict

The difficulty of deciding whether or not to have genetic testing at the time of decision, was retrospectively assessed using the traditional format of the Decisional Conflict Scale.[138,139] 1 item ("I expect to stick to my decision") was left out as it is not applicable to DNA-testing.[137] 15 items scored from 0 'strongly agree' to 4 'strongly disagree' remained with excellent internal consistency (Cronbach's α=0.92). Scores were summed, divided by 15 and multiplied by 25 (scale 0–100); as defined by the test authors, scores <25 were considered as 'no decisional conflict', between 25 and 37.5 as 'moderate conflict' and ≥37.5 as 'severe conflict'. 1 DCS item "I am satisfied with my decision" (scale 0–4) was also used for overall satisfaction.

Family influence

Patients indicated whether the medical history of parents, sisters and brothers had influenced their decision, and specified the type of advice ('no advice', 'no DNA-test', 'wait with DNA-test', 'immediate DNA-test', 'other') received by individual relatives and friends. Patients also specified whose advice had the most influence on their decision, whether another person had been tested at the same time and whether this influenced their decision.

Reasons for DNA-testing

Open-ended questions assessed reasons for DNA-testing for *BRCA1/2* or Lynch syndrome.

Demographic and DNA-testing information

Demographics

Patients reported age, educational level, marital status and need for information (scale 1–10) in the surveys. History of psychological problems was collected from medical files, where such problems were recorded during standard genetic consultations.

DNA-testing characteristics

Age at and indications for DNA-testing were gathered from patient medical files: 1) pre-symptomatic, when there was a known family mutation but the patient has no cancer; 2) best available, when cancer was prevalent in the patient's family without a known mutation, but affected relatives were no longer available for testing; 3) patient affected with cancer at a young age with no known family mutation. DNA-results were also gathered: 1) mutation carrier; 2) definite non-carrier, known family mutation was not found in the patient; 3) inconclusive, no mutation was found in the patient as the first to be tested (but mutations in other still unknown genes may predispose to cancer).

Family history

In patient medical files information concerning family pedigrees was gathered to determine the presence of a known family mutation or cancer-affected parents, and the age of the youngest affected relative.

Psychological measures

Quality of Life

To measure global health-related quality of life (QoL), two items (scored 1–7, scale 2–14, α=0.82) were selected from the EORTC-QLQ-C30, which has been widely used and validated for cancer research.[127]

Coping style

The Threatening Medical Situations Inventory (TMSI[16]) assessed coping styles in hypothetical medical situations. A shortened version using two situations was previously validated[155,177] and chosen for length. Each situation is followed by three monitoring (seeking information) and three blunting (seeking distraction) statements, scored on a 5-point Likert-scale. Monitoring (M, α=0.61) and blunting (B, α=0.72) subscales were calculated by summing relevant item scores (each subscale 6–30).[155, 177] No classification methods were found in literature. However, as mean scores came out equal in initial analysis, subscales were combined to determine which coping style each responder showed a tendency towards: if the difference between scores was ≥4, responders

were classified as more blunting (B>M) or monitoring (M>B). If the difference was <4, responders were classified as neutral, unless one score was ≥24 (extreme cases). Thresholds were chosen to approximate a distribution of 25% B>M, 50% neutral and 25% M>B; all responders could thus be classified.

Impact of genetic testing for cancer

The Multidimensional Impact of Cancer Risk Assessment (MICRA[178]) focuses on specific psychosocial concerns following genetic testing for hereditary cancer. It consists of 19 items scored 0,1,3,5 and divided into three subscales: Distress (6 items, scale 0–30, α=0.77), Uncertainty (9 items, scale 0–45, α=0.75) and Positive Experiences (4 items, reverse scored, scale 0–20, α=0.62).[178]

Risk perception

A visual scale of 0–100 was used to measure lifetime risk perception of cancer occurrence for breast or colon cancer.

Experiences with genetic counseling and testing

Reactions to DNA-results

Overall psychological reaction to the DNA-results was assessed by one multiple choice item: 'the result did not keep me preoccupied' (no reaction), 'the result kept me preoccupied at first, but then I moved on' (short term), 'I needed a long time to process the result' (long term), or 'the result is still keeping me preoccupied' (ongoing).

Recommended age for DNA-testing

Patients specified the age at which they would recommend DNA-testing for hereditary cancer to other patients.

Satisfaction with genetic counseling

The QUOTE-gene(ca) questionnaire measures needs and preferences in genetic counseling for hereditary cancer.[140] A modified version including 18 items for types of services and 8 items for types of information[119] was reworded to assess whether these had been provided rather than desired (α=0.95). Each item is scored from 1 'not at all' to 4 'good'. Items were summed and divided by 26, to rate overall satisfaction on aforementioned scale.

Preventive measures for hereditary cancer

Surveillance advice following DNA-results ('none', 'familial', 'hereditary') was collected from medical files and compared to patient-reported use of cancer surveillance ('yes,

ongoing', 'yes, soon', 'no, too young', 'no, not necessary', 'no, do not want'). Yes/no questions evaluated satisfaction with the recommended surveillance scheme, desire to start surveillance before 25 years if a mutation carrier, desire to start surveillance if a non-carrier, and whether patients adjusted their lives in any other way (e.g. childbearing) due to DNA-results.

Statistical analysis

Patient characteristics and measures were analyzed using descriptive statistics. Decisional conflict was tested between groups: cancer syndrome (*BRCA1/2* vs. Lynch), gender (male vs. female) and mutation status (carrier vs. non-carrier). Further comparisons of measures were made based on moderate-severe versus no decisional conflict. Continuous variables were tested using the unpaired t-test, ordinal variables using the Mann-Whitney U test, nominal/dichotomous values using the chi-square/Fisher's Exact test. To evaluate the influence of more than one variable on decisional conflict, multiple backward (Wald) logistic regression was applied. The probability level for statistical significance testing was set at 0.05 (two-tailed). The SPSS 18.0 statistical package was used to analyze the data.

RESULTS

Comparing responders (n=111) to non-responders (n=108), 36% of 45 males and 55% of 174 females returned the survey ($p<0.03$). No further differences (age at DNA-testing, current age, cancer syndrome, indication for DNA-testing, mutation status, family history, surveillance advice) were found. Median age of responders was 27 [21–40] and 86% were female. Three-quarters of responders (73%) were tested for *BRCA1/2* mutations, 27% for Lynch syndrome; 42% were confirmed as a mutation carrier (Table 1).

Decision-making

Regret

Most responders had no regret (97%: scored 1 on scale 1–4) and 95% would make the same choice, whereas 4% would start DNA-testing at a later moment and 1% would not at all. No differences were found based on decisional conflict (see below).

Decisional conflict

A total of 39% of responders reported either moderate (DCS 25–37.5: 32%) or severe (DCS≥37.5: 7%) decisional conflict. The majority of responders (98%) was satisfied with their choice (scored 3–4 on scale 0–4), 58% strongly so (scored 4). Patients reporting

Table 1: General, DNA-testing and family history characteristics of all responders (n=111) tested for *BRCA1/2* or Lynch syndrome at age 18-25 years: % or median [range].

GENERAL CHARACTERISTICS	
Current age	27 [21-40]
Age at DNA-testing	23 [18-25]
Years since DNA-testing	4 [0-15]
Education level	
- low	11%
- medium	46%
- high	43%
Marital status	
- married/registered cohabitation	28%
- unregistered relationship	55%
- single	17%
Need for information (1-10)	9 [1-10]
Recorded history of psychological problems	6%
DNA-TESTING CHARACTERISTICS	
DNA-testing for	
- *BRCA1/2*	73%
- Lynch syndrome	27%
Indication for DNA-testing	
- presymptomatic (mutation in family)	76%
- index patient: best available	19%
- index patient: affected at young age	5%
DNA-test result	
- mutation carrier	42%
- definitive non-carrier	36%
- inconclusive non-carrier	22%
FAMILY HISTORY CHARACTERISTICS	
Presence of mutation in the family	
- unknown	24%
- known on maternal side	41%
- known on paternal side	35%
Age of youngest relative with cancer	34 [18-53]
Mother affected with cancer	48%
Father affected with cancer	14%

moderate-severe decisional conflict were less convincingly satisfied with their choice ($p<0.001$): only 17% strongly agreed, 78% agreed, and 5% was neutral, whereas 84% of responders without conflict strongly agreed and 16% agreed. There were no differences in decisional conflict based on cancer syndrome, gender or mutation status.

Family influence

The majority of responders (78%) had been influenced by the medical history of their parents, versus 13% by that of sisters and 1% of brothers. Nearly half of responders had received no advice from relatives or was supported in making their own choice (45%), followed by 'immediate DNA-test' (41%). Persons of most influence are shown in Figure 1. In 43%, another relative was simultaneously tested, but only 15% indicated this had influenced their decision.

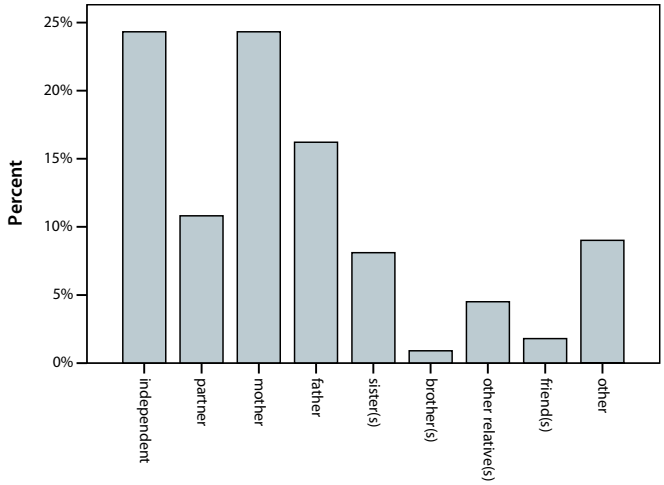

Figure 1: Person of most influence on the decision-making process as reported by all responders (n=111) tested for *BRCA1/2* or Lynch syndrome at age 18-25 years. Multiple choice options focused on individual first degree family members and partner.

Reasons for DNA-testing

As multiple reasons were possible per responder, percentages are not cumulative: half (47%) included an emotional reason for DNA-testing, most importantly the need for certainty. Other reasons were family history (44%), preventive measures (24%) and (future) children (14%).

Demographic and DNA-testing information

Demographics and DNA-testing

Demographic and DNA-testing characteristics are shown in Table 1.

Family history

Family history characteristics are shown in Table 1: 76% had a known family mutation. Those with decisional conflict were more likely to have a lower age of the youngest affected relative ($p<0.04$), a known family mutation on the paternal side ($p<0.04$) or an affected father ($p<0.05$).

Psychological measures

Quality of Life (QoL)

Median overall QoL was high at 12 [5–14] (scale 2–14). No significant differences in QoL were found between patients with and without decisional conflict.

Coping style

Nearly a third (29%) were classified as leaning more towards monitoring coping style, versus 25% more blunting and 46% neutral. As shown in Figure 2, there were more

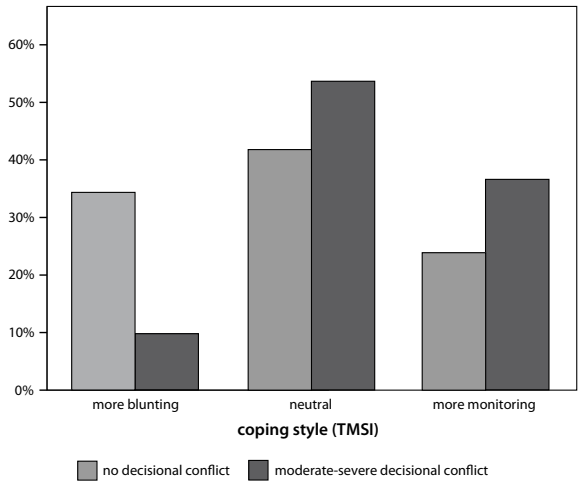

Figure 2: Coping style (TMSI) of young adults tested for *BRCA1/2* or Lynch syndrome at age 18-25 years, in responders with no versus moderate-severe decisional conflict. Coping style was classified as a tendency towards more blunting (seeking distraction when faced with a threat), more monitoring (seeking information) or neutral.

responders leaning towards monitoring or neutral in responders with vs. without decisional conflict ($p<0.02$).

Impact of genetic testing for hereditary cancer

Psychological impact did not differ based on decisional conflict, with overall low median scores of 5 [0–24] for Distress (scale 0–30), 6 [0–27] for Uncertainty (scale 0–45) and 5 [0–20] for Positive Experiences (scale 0–20).

Risk perception

Median risk perception for breast/colon cancer was 45 [0–100] (scale 0–100) and did not differ based on decisional conflict.

Experiences with genetic counseling and testing

Reactions to DNA-results

Most responders reported no (42%) or short term (46%) psychological reactions following DNA-results, 6% reported long term and 6% ongoing reactions. No differences were found based on decisional conflict.

Satisfaction with genetic counseling

Counseling information and services were considered sufficient (median 3.3 [1.4–4.0], scale 1–4). There were no differences based on decisional conflict.

Recommended age for DNA-testing

2% of responders would recommend DNA-testing from birth, 4% from 16 years, 24% from 18 years, 20% from 20 years, 18% from an age between 21-24 years, 18% from 25 years and 2% from 30-35. 12% of responders did not report an age as this depended on the person.

Prevention measures for hereditary cancer

The majority (84%) was satisfied with their surveillance scheme and 25% reported other life adjustments (e.g. earlier childbearing) due to their DNA-results. 88% were following surveillance advice correctly, 9% started surveillance earlier and 3% considered surveillance unnecessary despite familial advice. Many (77%) desired surveillance measures before age 25 if a mutation carrier and over half (59%) desired surveillance when no mutation was found. No differences based on decisional conflict were found.

Multifactorial analysis of decisional conflict

To assess the influence of multiple variables on decisional conflict, backward (Wald) logistic regression was performed using the four most significantly different variables from univariate analyses. Age of youngest affected relative and affected father were not significant, leaving only coping style and family mutation as variables related to decisional conflict. The strongest factor was coping style: responders with more monitoring (OR 5.71 [1.47–22.25]) or neutral coping style (OR 5.08 [1.45–17.8]) were over 5 times more likely to report decisional conflict than those leaning more towards blunting ($p<0.03$). Those with a paternal family mutation (OR 4.10 [1.46–11.55]) or unknown family mutation (OR 3.14 [1.02–9.67]) were also more likely to report decisional conflict than those with a maternal family mutation ($p<0.02$). This model was statistically significant with $\chi 2$ (4, $n=101$) = 17 ($p=0.002$), explaining 22% of the variance in decisional conflict and correctly classifying 68% of cases.

As coping style was of strongest influence, additional univariate analyses were performed comparing responders with more monitoring/neutral coping style versus more blunting: beyond a higher need of information in those with more monitoring/neutral coping ($p<0.02$), no significant differences were found. Conversely, comparing responders with more blunting/neutral coping style versus more monitoring, showed a lower desire for surveillance as a non-carrier in those leaning more towards monitoring ($p<0.04$), but no further differences.

DISCUSSION

It can be concluded that for the majority of young adults older than 18 years, it is not necessary for clinical geneticists to raise the DNA-testing age for *BRCA1/2* or Lynch syndrome from 18 to 25 years, which is the age to start surveillance. Most responders in our study were satisfied with their former decision and had no regrets of DNA-testing at a younger age. In fact, 68% would recommend other patients to do so, with only 20% recommending after 25 years. However, a third did report decisional conflict, especially those patients who tended to actively seek information when faced with a threat (monitoring to neutral coping style), or with a paternal or unknown inheritance. Decisional conflict also lowered the rate of satisfaction with the choice made, but did not coincide with regret, suggesting that these are separate entities when assessed retrospectively. The process of genetic counseling/testing appears to have been effective in preventing those experiencing decisional conflict from regretting their final decision. In fact, genetic counseling likely helped to select those young adults less likely to react adversely to DNA-results, prior to the decision to start DNA-testing.

Young adults are known to be sensitive to social influence from family members.[47,48] Medical history of parents did influence decision-making for most young adults in our study. Half of the young adults felt supported by their family in making their own decision. Almost a quarter even specified having made their own independent choice, rather than pointing out another person as most influential. Genetic counselors could take advantage of such social support by encouraging young adults before 25 years to discuss DNA-testing with their adult relatives, who could provide the cognitive skills they have not yet fully developed.

Previous studies have shown a positive correlation between age and monitoring coping style[174,179] thus younger patients are expected to make less use of monitoring. However, 29% of young adult responders had a tendency towards more monitoring than blunting at the time of the study. Coping style may change over time depending on life events[179]: patients leaning towards blunting at the time of decision-making may lean more towards monitoring as a result of DNA-testing, as they become more aware of their health risks. It is also possible that those with a tendency for monitoring are more likely to start DNA-testing, while those showing more blunting delay or avoid DNA-testing altogether.[173] In this retrospective study, it was not possible to differentiate between these two options.

Regardless, current tendency towards more monitoring or neutral coping style was the strongest factor contributing to former decisional conflict. This could be due to patients leaning towards monitoring finding information about both benefits and disadvantages of genetic testing at their age. Patients leaning towards blunting may be more likely to remain (deliberately) ignorant of these disadvantages. Paternal inheritance of a known family mutation also influenced decisional conflict. Cancers in the paternal family are generally underreported, possibly because males are less likely to communicate about family health matters.[180] Patients reliant on a male relative may not know details of (hereditary) cancer prevalence. Similarly, when there is no known family mutation, patients may be less aware of their precise family history or the full consequences of a hereditary predisposition. Especially when such information is actively sought after (monitoring) but not easily available, decisional conflict may occur.

Responders were satisfied with the process of genetic counseling/testing and recommended surveillance scheme, the majority showing no to short term psychological reactions following DNA-results and adhering to surveillance advice. Despite high satisfaction and adherence, many (77%) did report a desire for surveillance to start before 25 years if a mutation was found. Responders leaning towards monitoring showed less desire for surveillance as a non-carrier than those with more blunting or neutral coping

style. This suggests that, while the higher rate of decisional conflict might warrant additional support for young adults leaning towards monitoring, further follow-up does not seem required for those who turn out to be non-carriers after testing.

Our study is limited by a possible selection bias due to low response rate (51%) and significantly fewer males responding ($p<0.03$). This is unsurprising: both males and younger patients are known to have lower participation rates in survey-based studies.[181] Another limitation is the retrospective nature of our study, which is sensitive to recall bias and perception bias such as cognitive dissonance reduction: exaggerating benefits of an unpleasant experience to achieve peace-of-mind thus reporting less regret.[182] This may similarly limit our study's ability to reflect on decisional conflict at the time of the actual decision to start genetic testing.[137] To our knowledge, decisional conflict has not been studied before in this particular age group within the context of genetic testing, therefore it is not possible to evaluate differences due to the retrospective measurement. However, as one third of our study sample reported moderate to severe decisional conflict contrary to a mere 3% reporting regret, possibly decisional conflict is influenced less by such perception bias.

Having decisional conflict did not correlate with a more adverse impact of genetic testing, nor were there differences in decisional conflict comparing mutation carriers vs. non-carriers. This suggests that decisional conflict is an independent process, not influenced by DNA-results, which are unknown at the time of decision-making. Decisional conflict could then be a target for future interventions. While standardized support by a social worker during the decision-making process is currently provided, this support could be made more effective by focusing on those young adults experiencing decisional conflict and their specific needs. Exploring coping style and the presence of a family mutation may help genetic counselors to identify those young adults in need of such support.

In conclusion, our study shows that it is not necessary to change the age of DNA-testing for *BRCA1/2* mutations or Lynch syndrome, as very few reported regret and many desired DNA-testing before 25 years.

Chapter 7

Patient experiences following gene panels based on exome sequencing in clinical diagnostics: high acceptance and low distress

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ABSTRACT

Introduction: The Radboud university medical center was amongst the first to implement two-step exome sequencing in clinical genetic diagnostics. This study is the first to evaluate patient experiences with gene panels based on exome sequencing, using quantified psychological variables: acceptance, psychological distress, expectations of heredity and unsolicited findings.

Methods: Between August 2011 and July 2012, 177 patients diagnosed with early-onset colorectal/kidney cancer, deafness, blindness or movement disorder consented to diagnostic exome sequencing offered by clinical geneticists. Baseline questionnaires were sent to 141 adults, returned by 111 with median age of 49 [22–79] years and positive family history in 81%. Follow-up included 91 responders at median 4 [2–22] weeks after results from known gene panels per diagnosis group; exome-wide analysis is ongoing.

Results: Confirmed or possibly pathogenic mutations were found in 31% with one unsolicited finding (oncogenetic panel). Most patients (92%) were satisfied. There were no significant changes in heredity-specific distress (18% at baseline, 17% at follow-up) and expectations of heredity. Fewer patients expected unsolicited findings at follow-up (29% versus 18%, p=0.01). Satisfaction and distress was equal in those with versus without mutations.

Conclusion: Most adults accepted and were satisfied with gene panels based on diagnostic exome sequencing, few reporting distress.

Keywords

distress – exome – gene panels – genetic – next generation – patient experiences – sequencing

INTRODUCTION

Next generation sequencing e.g. exome sequencing has great potential to identify the genetic cause of numerous diseases[183] with increasing implementation in clinical diagnostics.[2] Diseases may be suspected of heredity (e.g. positive family history or early onset) but show high genetic heterogeneity[52,184-186]: conventional sequential single-gene testing of many candidate genes is time-consuming.[2,56] Exome sequencing allows simultaneous testing of all genes and could lead to rapid identification of a genetic cause or new gene discoveries.[2] An early genetic diagnosis could preclude further diagnostic testing and provide more information about prognosis and family consequences.[186]

Diagnostic exome sequencing is expected to have major impact on clinical genetic testing. However, counselors and patients should consider possible unclear results (variants possibly but not clearly pathogenic) or unsolicited findings for unrelated diseases, the frequency and nature of which are unknown.[53] Handling these unsolicited findings is a main ethical concern for diagnostic implementation of exome sequencing.[53] To limit possibility of unsolicited findings, the Radboud university medical center (Radboudumc) implemented two-step diagnostic exome sequencing within the Human Genetics department.[56] Clinically affected patients at increased risk of an underlying genetic cause of their disease, were offered oral pre-test genetic counseling and written information leaflets by clinical geneticists. Patients were informed that exomes were fully sequenced, but initial analysis was targeted only at referral disease-causing gene panels (step 1). Identified mutations were reported back to the patient as confirmed or possibly pathogenic. If no mutations were identified, patients were informed and exome-wide analysis followed (step 2: opt-out not possible). Counseling included that unsolicited findings (e.g. cancer predisposition in a deafness patient) were possible especially in exome-wide analysis, but exact probabilities and type of findings could not be predicted. Such findings were discussed in a multidisciplinary advisory board to determine clinical relevance, before disclosure to the clinical geneticist, who then informed the patient.[53] Patients who agreed to be informed about potential unsolicited findings, started exome sequencing after consent was obtained. Patients declining information about clinically relevant unsolicited findings were excluded from exome sequencing, instead offered single-gene testing.

Psychological effects of conventional genetic testing have been studied mainly in hereditary cancer. In colorectal cancer patients, 25% reported distress before and 13% after genetic counseling: mutation carriers showed higher distress than non-carriers, but these scores returned to baseline levels over time[108]; similar results were found in breast cancer patients.[117] This study is the first to quantify patient experiences in exome se-

quencing, using standardized psychological questionnaires. As opt-out of exome-wide analysis was not possible, participants in this study must consider possible unclear or unsolicited findings in acceptance and expectations of exome sequencing throughout the two-step procedure. If a similar trend to conventional genetic testing can be found, this may lower hesitancy amongst professionals to implement exome sequencing in clinical diagnostics and inform discussion regarding appropriate consent procedures.

In literature regarding conventional genetic testing in hereditary cancer, van Oostrom e.a.[15] applied Leventhal's common sense model of self-regulation and psychological adjustment, using illness perception as the basis for coping responses (monitoring i.e. actively seeking information, and blunting i.e. passively seeking distraction[16]) and psychological well-being. Pessimistic illness perception related to high risk perception (i.e. expectations), causal attribution to genetic factors and passive coping, relating to hereditary cancer distress.[15] These may also be contributory factors to distress in exome sequencing and determined this study's psychological measures.

The hypothesis of this prospective observational study is that many patients accept two-step diagnostic exome sequencing, without increased distress or altered expectations after results from known disease-causing gene panels, similar to current experiences in conventional genetic testing.

MATERIALS AND METHODS

Genetic procedure

The Radboudumc Human Genetics department implemented diagnostic exome sequencing for diseases with high heterogeneity and local expertise.[2,55,56] Technical specifications on exome sequencing and variant interpretation were described previously.[55,56] This study focused on adults with early-onset (<40 years) colorectal or kidney cancer, deafness, blindness or movement disorders.

Gene panels per diagnosis were designed by multidisciplinary expert teams and published previously.[56] The cancer gene panel covered all known hereditary cancer syndromes as association with secondary cancer types may change (e.g. urothelial bladder cancer in *MSH2*-related Lynch syndrome[187]): including all cancer genes was considered more effective. Actionable unsolicited findings within this panel were considered immediately clinically relevant for patient disclosure, without consultation of an independent board.

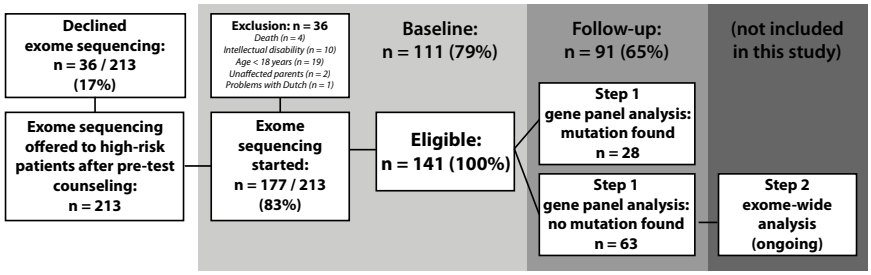

Figure 1: Flowchart of patient inclusion and questionnaire response at baseline and follow-up amongst adult patients consenting to diagnostic exome sequencing.

Between August 15th 2011 and July 15th 2012, 213 patients diagnosed with one of these four diseases were selected by clinical geneticists for an increased risk of a genetic cause of their disease (e.g. positive family history, early onset) and offered diagnostic exome sequencing after pre-test genetic counseling. Of these, 36 (17%) declined and 177 (83%) gave written informed consent to start exome sequencing (Figure 1).

Study procedure

This prospective observational study was required by the local medical ethical board to recruit only patients consenting to exome sequencing, limited by clinical lab capacity (maximum n=50 per group). Exclusion criteria were: death (n=4), age <18 years (n=19), healthy parents of an affected child (n=2), intellectual disability (n=10) or problems with Dutch text (n=1). 141 patients were eligible (Figure 1). Most (78%) had undergone previous single-gene testing which did not identify pathogenic mutations. Patients were invited by mail for an online or paper baseline questionnaire (n=34 mail reminders): 111 (82%) baseline questionnaires were returned. Two-three weeks following gene panel result disclosure (step 1), follow-up questionnaires were sent (n=30 reminders): 91 (65%) were returned median 4 [2–22] weeks after disclosure. Exome-wide analysis (step 2) is ongoing and not included in this study. In two patients, exome sequencing (thus follow-up) was halted due to a (possible) diagnosis in affected relatives.

Primary study variables included satisfaction and regret at follow-up on 4-point Likert-scales ('not at all' to 'very much'). Participants also considered the hypothetical situation of making their decision again: 'exome sequencing', 'no exome sequencing' or 'do not know'. These questionnaires were developed in previous studies.[151,156] Heredity-specific distress was assessed at baseline and follow-up by the Impact of Event Scale (IES[132,133], range 0–75, Cronbach's α in this study=0.92–0.93, threshold ≥26 for clinical relevance) adapted for a possible hereditary disease as the traumatic event.

Secondary study variables included expectations of heredity (finding a genetic cause and finding the same disease in family members) measured at baseline and follow-up by visual numerical scales of 0–100 and verbal 5-point Likert-scales ('very low' to 'very high') based on breast cancer risk perception measurements.[188] Perceptions of hereditary and non-genetic aetiologies were assessed as yes/no items to simplify data analyses. Expectations of unsolicited findings were also measured at baseline and follow-up by numerical 0-100 and verbal 5-point scales. Data on age and educational level were gathered from questionnaires, medical history data and gene panel results (including unsolicited findings) were summarized from medical files. Coping style was measured at baseline using the short version of Threatening Medical Situations Inventory (TMSI[16,155], monitoring subscale α=0.66, blunting subscale α=0.52) to categorize patients as used in a previous study.[15] Quality of life was assessed by the global health status subscale from the EORTC-QLQ-C30 (0–100, α=0.89–0.93[127,128]) and general psychological distress by the 12-item General Health Questionnaire (GHQ-12[129], 0–12, α=0.90–0.88, threshold ≥3[130]). Illness perception was measured using the Brief Illness Perception Questionnaire (B-IPQ[189,190]) modified for average score of only items considered applicable by the participant (0–10, α=0.48–0.56). The impact of genetic testing was assessed by the Multidimensional Impact of Cancer Risk Assessment (MICRA[178]) after removing 5 cancer-specific items: renamed MIHRA for Hereditary Risk Assessment with subscales Distress (0–30, α=0.85), Uncertainty (0–20, α=0.58), Positive Experiences (0–20, reverse scored, α=0.56), Illness (0–10, α=0.16) and, if applicable, Children (0–10, α=0.63).

Decision making and reactions were assessed using questionnaires from previous studies.[151,156] Open-ended questions assessed participants' reaction to the offer of and reasons for starting exome sequencing (>10% reported). Initial expectations of exome-results were reported retrospectively at follow-up: 'illness is hereditary', 'illness is not hereditary', 'no expectations' or 'other'. Participants indicated emotional reactions to gene panel results: positive, negative and neutral. Psychological reaction was assessed by one multiple choice item: 'not applicable: testing ongoing', 'result did not keep me preoccupied' (no reaction), 'result kept me preoccupied at first, but then I moved on' (short-term), 'I needed a long time to process the result' (long-term), or 'result still keeps me preoccupied' (ongoing). Participants specified advice to others: 'exome sequencing', 'single-gene testing', 'no DNA-testing at all' or 'do not know'.

Statistical analysis

Following descriptive statistics, baseline versus follow-up results were compared using the paired t-test for continuous, Wilcoxon test for ordinal and McNemar's test for nominal variables. Follow-up results were compared between responders with versus without (confirmed or possibly pathogenic) mutations, using the independent t-test

for continuous, Mann-Whitney U test for ordinal, and chi-square/Fisher's Exact test for nominal variables. Repeated measurements ANOVA was used to compare responders with versus without mutations (result) from baseline to follow-up (time). Correlations between expectations of heredity, expectations of unsolicited findings, heredity-specific distress, coping style and illness perception were assessed by Spearman's Rank Correlation (Spearman ρ). The probability level for statistical significance testing was set at 0.05 (two-tailed). The SPSS 20.0 statistical package was used to analyze the data.

RESULTS

Demographics of baseline responders are shown in Table 1. Median age was 49 [22–79] years, male/female ratio was 1:1 and 81% had a positive family history; 25% were diagnosed with cancer, 26% deafness, 15% blindness, 34% movement disorders. Baseline responders (n=111, 79%) were older than non-responders (n=30) with median 49 [22–79] versus 42 [20–66] years (p=0.01) and more likely to have a positive family history (81% versus 60%, p=0.03). Males and females did not differ at baseline. Confirmed or possibly

Table 1: Sociodemographic, family and informational characteristics of all baseline responders (n=111) consenting to diagnostic exome sequencing.

Characteristic	N (%) or median [range]
Age at inclusion (years)	49 [22-79]
Female gender	55 (50%)
Education level	*n=109:*
- low	49 (45%)
- medium	27 (25%)
- high	33 (30%)
Diagnosis	
- colorectal or kidney cancer <40yrs	27 (25%)
- deafness	29 (26%)
- blindness	17 (15%)
- movement disorders	38 (34%)
Previous genetic testing	90 (81%)
Positive family history	90 (81%)
Affected relatives	
- parent(s)	48 (43%)
- sibling(s)	50 (45%)
- child(ren)	16 (14%)
- 2nd degree	46 (41%)
- ≥3rd degree	28 (25%)
Coping style	
- more blunting	29 (28%)
- neutral	57 (55%)
- more monitoring	17 (17%)

pathogenic mutations in known gene panels were identified in 31% of 91 follow-up responders. Those with versus without mutations were less likely to have had previous genetic testing (63% versus 92%, p=0.01); no differences were found in family history. There was one *FH*-mutation (hereditary leiomyomatosis, renal cell cancer) found unrelated to a patient's colorectal cancer diagnosis. This unsolicited finding was considered immediately clinically relevant for patient disclosure.

Satisfaction

Most responders (92%) were moderate-highly satisfied, only 3% reported regret. 89% would start exome sequencing again; 11% were uncertain, not being aware of alternatives or depending on estimated heredity, waiting time or health benefits. No differences were found comparing those with versus without mutations. Dissatisfaction or regret were due to the long lag time until gene panel results were available (median 9 [5–16] months from intake consultation to result disclosure).

Heredity-specific distress

Clinically relevant heredity-specific distress (IES≥26) was reported in only 18% at baseline, equal to 17% at follow-up (Figure 2). No differences were found comparing participants with versus without mutations at baseline and follow-up; mean scores remained below clinical relevance (Table 2), as did the score of the patient with an unsolicited finding. Heredity-specific distress was not correlated to coping style or expectations

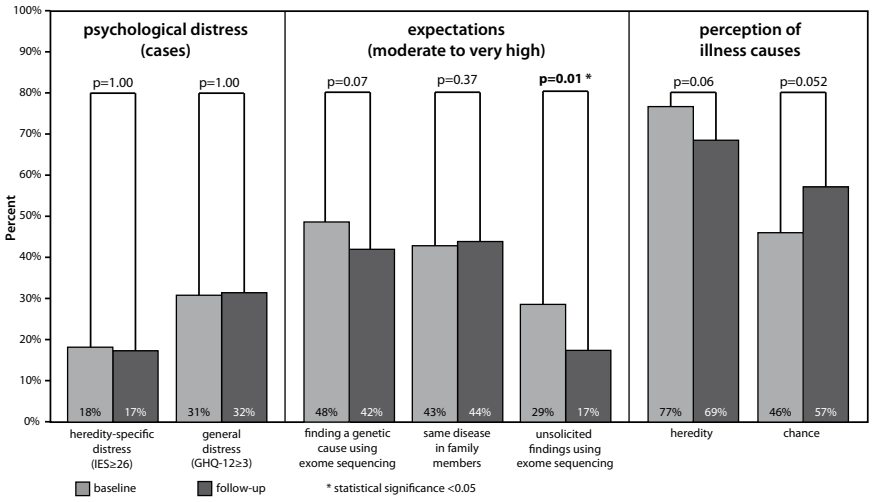

Figure 2: Psychological distress, expectations and perception of illness causes in adult patients consenting to diagnostic exome sequencing, at baseline (n=111) versus follow-up (n=91).

Table 2: Psychological outcomes of all follow-up responders (n=91) consenting to diagnostic exome sequencing, comparing those with confirmed or likely pathogenic mutations (n=28) versus those without mutations (n=63) identified in known disease-related gene panels based on exome sequencing.

Characteristic	Baseline		Follow-up		Repeated measurements ANOVA		
	Mutation: mean±SD	No mutation: mean±SD	Mutation: mean±SD	No mutation: mean±SD	P: interaction time*result	P: main effect time	P: main effect result
Heredity-specific distress (IES: 0-75)	11.4±13.8	12.6±13.9	9.6±13.6	11.3±13.1	*0.94*	*0.19*	*0.71*
General distress (GHQ-12: 0-12)	2.3±3.4	1.9±2.8	2.3±3.5	1.9±2.6	*0.80*	*0.84*	*0.54*
Expectation of finding a genetic cause of illness using exome sequencing (0-100)	68.9±19.4	55.1±22.3	68.6±23.4	44.2±24.9	*0.09*	*0.20*	**0.00** *
Expectation of finding the same disease in family members (0-100)	68.8±25.3	51.6±31.1	65.6±27.8	48.0±28.6	*0.60*	*0.32*	**0.01** *
Expectation of unsolicited findings using exome sequencing (0-100)	57.8±27.1	47.1±20.5	50.2±27.1	38.5±20.6	*0.88*	**0.01** *	**0.01** *
Quality of Life (QoL: 0-100)	72.9±22.9	74.4±19.5	68.0±22.7	77.4±17.6	**0.03** *	*0.16*	*0.17*
Illness perception: overall score (modified B-IPQ: 0-10)	6.2±1.4	5.8±1.5	6.5±1.5	5.7±1.7	*0.35*	*0.46*	*0.07*
B-IPQ: consequences (0-10)	*n=26:* 8.4±1.7	*n=56:* 7.1±2.3	*n=27:* 8.2±1.9	*n=51:* 7.0±2.5	*0.60*	*0.60*	**0.02** *
B-IPQ: timeline (0-10)	*n=25:* 9.9±0.4	*n=47:* 9.4±1.5	*n=26:* 10±0.0	*n=51:* 9.2±2.1	*0.74*	*0.74*	**0.05** *
B-IPQ: personal control (reverse: 0-10)	*n=25:* 5.1±3.0	*n=49:* 5.7±2.9	*n=25:* 5.8±3.6	*n=56:* 6.1±3.2	*0.50*	*0.41*	*0.41*
B-IPQ: treatment control (reverse: 0-10)	*n=20:* 5.5±3.9	*n=43:* 4.5±2.9	*n=18:* 5.9±3.7	*n=46:* 4.6±3.2	*0.53*	*0.35*	*0.33*
B-IPQ: identity (0-10)	*n=24:* 6.3±3.8	*n=53:* 5.5±2.7	*n=24:* 6.5±3.3	*n=58:* 5.6±3.0	*0.17*	*0.65*	*0.09*
B-IPQ: concern (0-10)	*n=26:* 6.2±3.5	*n=55:* 5.8±3.1	*n=24:* 6.5±3.1	*n=60:* 5.9±3.1	*0.56*	*0.60*	*0.48*
B-IPQ: understanding (reverse: 0-10)	*n=24:* 2.6±2.9	*n=52:* 3.1±2.8	*n=25:* 2.8±2.9	*n=58:* 3.3±3.1	*0.97*	*0.43*	*0.51*
B-IPQ: emotional response (0-10)	*n=26:* 5.6±3.0	*n=56:* 5.3±2.8	*n=25:* 5.4±3.3	*n=59:* 5.4±2.9	*0.77*	*0.54*	*0.82*

* Statistical significance <0.05

of hereditary results or of unsolicited findings, but showed significant correlations to overall illness perception at baseline (ρ=0.29, p=0.01) and follow-up (ρ=0.22, p=0.04); specifically subscales concern (ρ=0.48, p<0.001), emotional response (ρ=0.38, p<0.001) and identity (ρ=0.24, p=0.02).

Expectations of heredity

Expectations of finding a genetic cause and of finding the same disease in family members did not differ comparing baseline with follow-up (Figure 2). Those with versus without mutations scored higher for both expectations at baseline and follow-up (Table 2, p=0.01). These expectations did not correlate to heredity-specific distress, coping style or illness perception. Causal perceptions did not differ (Figure 2).

Expectations of unsolicited findings

Expectations of unsolicited findings were lower at follow-up than baseline regardless of results (p=0.01, Figure 2, Table 2). Those with mutations did score consistently higher than those without (p=0.01, Table 2). There were no correlations between these expectations and heredity-specific distress, coping style or illness perception.

Psychological measures over time

General distress (GHQ-12) was equal at baseline and follow-up regardless of results (Figure 2, Table 2). Quality of life (QoL) was lower at follow-up versus baseline in those with mutations, but equal in those without mutations (Table 2). Overall illness perception was equal at baseline and follow-up but those with mutations experienced specifically more consequences (p=0.02) and longer duration (p=0.05) of their illness (Table 2). Impact of genetic testing (MIHRA: Table 3) was low.

Decision-making and reactions

Most responders (78%) reacted positively to the offer of exome sequencing. Reasons for exome sequencing were (multiple reasons possible, not cumulative): determine if heredity caused their disease (57%), children/family (42%), scientific progress (20%), possible prevention/treatment (16%) and no genetic cause found previously (14%). At follow-up, 40% reported initial expectations of exome-results to show their illness was hereditary, 32% had no expectations and 12% did not expect hereditary illness (16% other: e.g. more clarity in general). Those with versus without mutations were more likely to report retrospective expectations of hereditary illness (57% versus 32%, p=0.04). Few participants reported adverse reactions to gene panel results (Table 3). Most (78%) would recommend exome sequencing to others; only 2% recommended single-gene testing; 20% was uncertain, depending on the person or illness. No differences were found based on gene panel results.

Table 3: Reactions and impact of diagnostic exome sequencing results in all follow-up responders (n=91) after known disease-related gene panels based on exome sequencing.

Characteristic	N (%) or mean±SD
Impact of genetic testing (MIHRA)	
- subscore: Distress (0-30)	*n=86:* 5.2±6.0
- subscore: Uncertainty (0-20)	*n=88:* 3.0±3.5
- subscore: Positive experiences (0-20)	*n=85:* 10.7±4.9
- subscore: Illness (0-10)	*n=86:* 3.3±2.4
- subscore, if applicable: Children (0-10)	*n=66:* 5.5±3.3
Emotional reactions to gene panel results	*(non-cumulative)*
- positive (relieved, happy)	13 (14%)
- negative (sad, angry)	10 (11%)
- neutral (surprised, calm)	63 (69%)
Psychological reactions to gene panel results	
- not applicable: testing ongoing	56 (62%)
- no reaction	15 (16%)
- short term reaction	16 (18%)
- long term reaction	0 (0%)
- ongoing reaction	4 (4%)

DISCUSSION

The large majority of adult patients at high risk for hereditary disease, accepted two-step exome sequencing in a clinical diagnostic setting and were satisfied, reporting low distress following results from known disease-causing gene panels (step 1). Expectations of heredity did not change significantly, despite trends for lower expectations of finding a genetic cause and heredity causing their illness with more belief in random causality after gene panel results. However, before these results, patients with confirmed or possibly pathogenic mutations already had higher expectations of heredity and were less likely to have undergone previous genetic testing. They might have viewed their clinical and/or family history as more suggestive for hereditary disease, not having previously received negative results. Satisfaction or distress was equal to those without mutations. Relations between coping style and distress from literature[15] were not confirmed by our study. Heredity-specific distress instead correlated to illness perception, but not mutation status. Expectations of unsolicited findings were lower after gene panel results, although higher in those with versus without mutations; but in current results, unsolicited findings are less likely. We conclude that this novel two-step exome sequencing is acceptable to adult patients with normal intelligence, regardless of mutations found within known disease-causing gene panels. This sets the stage for continued evaluation of patient experiences following exome-wide analysis. Gene panels resulted in only one unsolicited finding without distress or dissatisfaction. Negative gene panel results low-

ered expectations of unsolicited findings, but also initiated exome-wide analysis which may uncover unsolicited findings farther removed from the referral disease.

Genetics is a fast-evolving field with many innovations within the genetic diagnostic process in which patient experiences have been studied before. For example, tumor genetic testing in colorectal cancer patients <50 years prior to genetic counseling was seen as valuable by patients without higher distress.[43] Breast cancer patients who were offered *BRCA*-mutation testing before genetic counseling, replacing the intake consultation with telephone, written and digital information, reported high satisfaction without increased distress.[151] Our current study supports that offering novel genome-wide tests may be acceptable to patients after pre-test counseling, despite concerns about adverse psychological effects. This is an important consideration for future clinical implementation of new genetic technologies. The study's main strength is the novel use of standardized psychological questionnaires to quantify early patient experiences with gene panels based on diagnostic exome sequencing. Patients reporting distress may require psychological follow-up, already incorporated in standard clinical genetic services through availability of specialized social workers or psychologists. As we conclude that the proportion of distressed patients is similar to numbers previously seen in conventional genetic testing[108], such standard care seems sufficient.

Although results of exome-wide analysis are yet to follow, our study thus far supports diagnostic exome sequencing as a two-step procedure, where initial analysis targets predefined gene panels, with the ability to expand beyond known genes, facilitating new gene discoveries. Our department chose exome sequencing with initial targeted data analysis of disease-specific gene panels, rather than disease-specific sequencing arrays. This allowed frequent updating of these panels, as all data were already sequenced thus ready for reanalysis, without new blood drawing.[2] Recently, our department allowed patients to opt out after gene panel analysis, offering the benefits of this new technique without the exome-wide risk of unsolicited findings.

A limitation of our study is including only patients who accepted diagnostic exome sequencing, as required by the local medical ethical board. Positive views were reported by those patients who opted in and may not be universally held, as 17% declined. It would be interesting to learn from this minority of patients, considering the current informed consent without opt-out for clinically relevant unsolicited findings. Most patients accepted exome sequencing including this risk, but some may have declined not wanting to know about (specific) unsolicited findings. Adjustments to the informed consent might be worth considering; this is up for debate within our department as well as in current literature.[53]

Our study results may be influenced by responders versus non-responders being older and more likely to have a positive family history. Patients with blindness (perhaps prohibiting patients from reading and filling in questionnaires) were underrepresented, making it impossible to compare diagnosis groups. However, the question "is there a genetic cause for my disease?" with implications for prognosis and family remains an overarching theme. The lack of impact on distress following results from gene panels based on diagnostic exome sequencing, may lower hesitations felt by genetic professionals in offering patients this new technique, allowing them to benefit from a higher diagnostic yield versus conventional single-gene testing, without concern for adverse psychological effects. As new genetic technologies continue to develop, likely starting with whole-genome sequencing, this provides support for clinical implementation of future innovations.

In conclusion, two-step exome sequencing in a clinical diagnostic setting is accepted by most adult patients, who report high satisfaction and low distress after results from predefined gene panels based on exome sequencing.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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STAGE III

Follow-up and prevention

"We may never understand illnesses such as cancer. In fact, we may never cure it. But an ounce of prevention is worth more than a million pounds of cure."

(David Agus)

Chapter 8

Regionale ziekenhuizen en UMC's vervullen verschillende behoeften in follow-up van *BRCA*-mutatiedraagsters

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ABSTRACT (ENGLISH)

Regional and university hospitals fulfill different needs in follow-up of *BRCA*-mutation carriers

Objective: Are there differences between *BRCA*-mutation carriers treated for prevention of breast cancer (BC) in a regional or university hospital?

Design: Retrospective observational study.

Method: Questionnaires were sent to 402 females between 25–60 years diagnosed with a *BRCA*-mutation in the Radboudumc (university medical center, UMC) between 2006–2012, then supported for surveillance in a regional hospital (RH follow-up) or the Radboudumc (UMC follow-up). Primary outcome measure was decisional conflict (DCS) i.e. doubt regarding BC prevention (preventive mastectomy (PM) or surveillance). Also, 105 oncologic specialists from 11 regional hospitals cooperating with the Radboudumc received questionnaires about the role of the UMC expert team regarding *BRCA*-care.

Results: 192 patients (48%) responded, of whom 80 (42%) were in RH follow-up and 112 (58%) in UMC follow-up. *BRCA*-mutation carriers in UMC follow-up reported more decisional conflict (median 17 [0–77] RH versus 25 [0–82] UMC, p=0.02) and information need (17% versus 35%, p=0.003); fewer chose PM (64% versus 40%, p=0.003). *BRCA*-mutation carriers in RH follow-up were more likely diagnosed with BC (39% RH versus 11% UMC, p<0.001). Among 47 regional specialists (response 45%), 47% had no experience consulting the UMC expert team; 70% preferred one-time UMC consultations for patients to discuss consequences for family relatives (89%) and prevention recommendations (83%).

Conclusion: *BRCA*-mutation carriers in RH versus UMC follow-up were different: women with BC more likely went or returned to regional hospitals, whereas women supported by the UMC expert team had more decisional conflict and/or information need and/or were presymptomatic.

Keywords
BRCA – hereditary – breast cancer – follow-up – risk management – surveillance – preventive surgery

SAMENVATTING

Doel: Zijn er verschillen tussen *BRCA*-mutatiedraagsters die voor preventie van mammacarcinoom (MC) begeleid worden in een regionaal ziekenhuis of UMC?

Opzet: Retrospectieve observationele studie.

Methode: Er werden vragenlijsten verstuurd naar 402 vrouwen tussen 25–60 jaar bij wie een *BRCA*-mutatie vastgesteld is in het Radboudumc (UMC) tussen 2006–2012, waarna zij voor surveillance begeleid werden in een regionaal ziekenhuis (RZ follow-up) of het Radboudumc (UMC follow-up). Primaire uitkomstmaat was decisional conflict (DCS) oftewel twijfel rondom MC preventie (preventieve mastectomie (PM) of surveillance). Daarnaast ontvingen 105 specialisten van 11 regionale ziekenhuizen die samenwerken met het Radboudumc vragenlijsten over de rol van het UMC expertiseteam met betrekking tot *BRCA*-zorg.

Resultaten: 192 *BRCA*-mutatiedraagsters (48%) respondeerden, waarvan 80 (42%) in RZ follow-up waren en 112 (58%) in UMC follow-up. *BRCA*-mutatiedraagsters in UMC follow-up rapporteerden meer decisional conflict (mediaan 17 [0–77] RZ versus 25 [0–82] UMC, p=0,02) en informatiebehoefte (17% versus 35%, p=0,003), waarbij zij minder vaak kozen voor een PM (64% versus 40%, p=0,003). *BRCA*-mutatiedraagsters in RZ follow-up waren vaker gediagnosticeerd met MC (39% RZ versus 11% UMC, p<0,001). Van 47 regionale specialisten (respons 45%) had 47% geen ervaring met overleg met het UMC expertiseteam; 70% gaf de voorkeur aan eenmalige UMC adviesgesprekken voor patiënten om gevolgen voor familieleden (89%) en preventieadviezen (83%) te bespreken.

Conclusie: *BRCA*-mutatiedraagsters die begeleid werden in een RZ tegenover UMC verschilden van elkaar: vrouwen met een MC gingen vaker (terug) naar de regio, terwijl vrouwen onder specialistische UMC begeleiding meer decisional conflict en/of informatiebehoefte hadden en/of presymptomatisch waren.

Sleutelwoorden

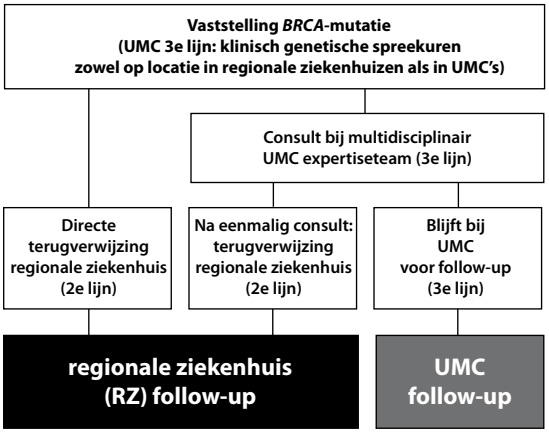
BRCA – erfelijk – mammacarcinoom – follow-up – risico management – surveillance – preventieve operatie

INLEIDING

BRCA1/2-mutaties worden verantwoordelijk geacht voor ongeveer 5-10% van de mammacarcinomen (MC) en ovariumcarcinomen (OvC).[31-33] Gezonde *BRCA*-mutatiedraagsters hebben een verhoogd levenslang risico op MC van 60-80% en op OvC van 30-60% bij *BRCA1* en 5-20% bij *BRCA2*.[31-33] Vanwege het verhoogde risico op mammacarcinoom wordt vanaf 25 jaar jaarlijks surveillance geadviseerd bestaande uit klinisch borstonderzoek en een MRI-scan met vanaf 30 jaar daarbij een mammografie.[61] *BRCA*-mutatiedraagsters ervaren mogelijk stress bij deze regelmatige controles in het ziekenhuis.[60] Zij kunnen kiezen voor een preventieve mastectomie (PM), wat het MC risico verlaagt tot minder dan 5%[154] maar fysieke en psychosociale gevolgen heeft op bijvoorbeeld lichaamsbeeldvorming en seksualiteit.[62] *BRCA*-mutatiedraagsters bij wie een MC wordt gediagnosticeerd kunnen kiezen (indien technisch mogelijk) voor een mammasparende operatie of mastectomie (unilateraal of bilateraal (contralateraal preventief)).[61] Na unilaterale behandeling is er een verhoogd risico op contralateraal mammacarcinoom tot 60%.[35] Gynaecologische surveillance (vaginale echoscopie en tumormerkstof CA125) voor OvC bleek niet effectief[63], hetgeen geleid heeft tot het advies van een risicoreducerende salpingooöphorectomie (RRSO): voor *BRCA1*-mutatiedraagsters tussen 35 en 40 jaar en voor *BRCA2*-mutatiedraagsters tussen 40 en 45 jaar.[61] Dit verlaagt het OvC risico met 69-100% met een klein restrisico op een primair peritoneaal carcinoom (waarvoor eveneens geen effectieve surveillance).[154]

De overlevingswinst van PM vergeleken met mammasurveillance is gering.[10] Het is aan *BRCA*-mutatiedraagsters zelf om, met de begeleidend specialist, voor- en nadelen af te wegen en een individuele keuze te maken. Ditzelfde geldt voor de timing van RRSO in relatie tot eventuele kinderwens. Vooral de keuze voor PM hangt samen met bepaalde patiëntkenmerken: jongere leeftijd, voorgeschiedenis van MC, kinderen, familieanamnese m.n. zus of moeder met MC.[67,191] *BRCA*-mutatiedraagsters kunnen twijfels hebben bij de besluitvorming rondom preventie (decisional conflict[138]), waarbij psychologische factoren zoals verwerkingsstrategie (omgaan met bedreigende informatie), stress en risicoperceptie mogelijk meespelen.[15] Ook worden preventiekeuzes beïnvloed door adviezen van artsen.[69] Adviezen verschillen tussen landen[70], medisch specialismen en artsen met meer of minder ervaring met genetisch testen.[71,72]

De zorg voor *BRCA*-mutatiedraagsters vindt plaats in de tweede- en derdelijns zorg. Genetische counseling en *BRCA*-testen vinden plaats bij UMC-gebonden afdelingen Genetica. Klinisch genetische spreekuren worden ook op locatie in regionale ziekenhuizen gehouden[192], veelal voor vrouwen met MC die als eerste in de familie getest worden. Presymptomatische vrouwen uit bekende *BRCA*-families worden vooral gezien en



Figuur 1: Zorgpaden na vaststelling van een *BRCA*-mutatie.

getest in het UMC. UMC's beschikken over multidisciplinaire *BRCA*-expertise teams, die *BRCA*-mutatiedraagsters adviesgesprekken aanbieden bij de gynaecoloog en internist of chirurg. Hierna volgt follow-up voor surveillance of preventieve operaties. Hiervoor worden *BRCA*-mutatiedraagsters verder begeleid in een regionaal ziekenhuis (mogelijk voorafgegaan door een eenmalige UMC consult) of het UMC (Figuur 1). De vraag is of de huidige *BRCA*-zorg verschilt tussen regionale ziekenhuizen en UMC's wat de continuïteit van deze zorg zou kunnen belemmeren, en hoe de samenwerking geoptimaliseerd kan worden.

Het doel van deze studie is om *BRCA*-mutatiedraagsters begeleid in regionale ziekenhuizen te vergelijken met vrouwen begeleid in het UMC door de evaluatie van hun besluitvorming en keuzes rondom MC preventie. Ook worden regionale specialisten benaderd over de samenwerking met het UMC rondom *BRCA*-zorg.

METHODEN

BRCA-mutatiedraagsters

Studiepopulatie

Vrouwen van 25 tot 60 jaar bij wie een *BRCA*-mutatie is vastgesteld tussen 2006–2012 bij de afdeling Genetica van het Radboudumc (UMC), kregen in februari 2014 een eenma-

lige vragenlijst en werden gecategoriseerd in: regionale ziekenhuis (RZ) follow-up en UMC follow-up (Figuur 1).

Primaire uitkomstmaat

Decisional conflict (DCS[138]) rondom MC preventie.

Secundaire uitkomstmaten

Algemene (o.a. leeftijd, opleidingsniveau, verwerkingsstrategie (TMSI[155,156])) en klinische kenmerken (m.n. bekende of nieuw ontdekte *BRCA*-familie, diagnose MC, wel/geen PM), inschatting *BRCA*-expertise (meerwaarde UMC) en besluitvorming (invloeden, shared decision making, spijt van keuzes (DRS[193])). Psychologische maten waren MC-specifieke stress (IES/SVL[133]), impact van genetisch testen (MICRA[178]), lichaamsbeeld, seksueel functioneren/plezier (uit EORTC-QRQ-BR23[194]) en MC risico perceptie voor en na PM. Verbeterpunten voor samenwerking tussen regionale ziekenhuizen en UMC's werden geïnventariseerd als open vraag.

Regionale oncologische specialisten

Studiepopulatie

De afdeling Genetica van het Radboudumc heeft samenwerkingsverbanden met 11 regionale ziekenhuizen in zuidoost Nederland voor spreekuren op locatie. Medisch oncologen, chirurgen en gynaecologen van deze ziekenhuizen ontvingen per post een vragenlijst.

Uitkomstmaten

Ervaring met overleg UMC expertiseteam; voorkeur voor directe terugverwijzing, eenmalig consult of overname van de zorg van de *BRCA*-mutatiedraagsters; welke onderwerpen moet het UMC expertiseteam met *BRCA*-mutatiedraagsters bespreken; gewenste ondersteuningsmiddelen; MC/OvC preventie adviezen voor *BRCA*-mutatiedraagsters, met of zonder diagnose MC.

Statistische analyses

Resultaten van vragenlijsten van *BRCA*-mutatiedraagsters en regionale specialisten werden als beschrijvende statistieken gerapporteerd. Patiëntkenmerken werden vergeleken tussen responders versus niet-responders, responders in RZ follow-up (met of zonder eenmalig UMC consult: geen relevante verschillen) versus UMC follow-up, en responders mét versus zonder MC diagnose, met onafhankelijke t-toets voor continue, Mann-Whitney U toets voor ordinale en chi-kwadraat toets voor nominale variabelen. Multivariate logistische regressie analyse van RZ versus UMC follow-up werd uitgevoerd

Tabel 1: Algemene kenmerken (N (%) of mediaan [range]) van *BRCA*-mutatie draagsters (n=192) verdeeld op locatie van begeleiding voor MC preventie: 1) regionale ziekenhuis (RZ) follow-up en 2) UMC follow-up; en verdeeld op wel of geen diagnose mammacarcinoom (MC).

Kenmerk	Totaal (n=192)	Verdeling: locatie MC preventie			Verdeling: diagnose MC		
		RZ (n=80)	UMC (n=112)	p-waarde	Wel MC (n=51)	Geen MC (n=141)	p-waarde
Mutatie							*1,000*
- *BRCA1*	122 (64%)	34 (69%)	67 (60%)	*0,226*	32 (63%)	90 (64%)	
- *BRCA2*	70 (36%)	15 (31%)	45 (40%)		19 (37%)	51 (36%)	
Diagnose mammacarcinoom (MC)	51 (27%)	39 (39%)	12 (11%)	*<0,001 **			*n.v.t.*
Diagnose ovariumcarcinoom (OvC)	2 (1%)	1 (1%)	1 (1%)	*n.v.t.*	1 (2%)	1 (1%)	*n.v.t.*
Leeftijd bij *BRCA*-uitslag	41 [21 – 57]	42 [21 – 57]	38 [21 – 56]	*0,07*	46 [25 – 57]	38 [21 – 57]	*<0,001 **
Leeftijd bij inclusie	45 [25 – 61]	47 [25 – 61]	44 [25 – 60]	*0,09*	49 [28 – 61]	43 [25 – 60]	*<0,001 **
Aantal jaren sinds *BRCA*-uitslag	4 [0 – 8]	4 [0 – 8]	4 [1 – 8]	*0,32*	3 [0 – 8]	4 [1 – 8]	*0,01 **
Opleidingsniveau	*n=191:*	*n=79:*		*0,07*	*n=50:*		*0,001 **
- hoog	62 (33%)	24 (30%)	38 (34%)		12 (24%)	50 (35%)	
- midden	65 (34%)	20 (25%)	45 (40%)		9 (18%)	56 (40%)	
- laag	64 (33%)	35 (44%)	29 (26%)		29 (58%)	35 (25%)	
Behoefte aan informatie (1-10)	8 [1 – 10]	8 [1 – 10]	8 [1 – 10]	*0,35*	8 [4 – 10]	8 [1 – 10]	*0,98*
Verwerkingsstrategie (TMSI)	*n=182:*	*n=76:*	*n=106:*	*0,003 **	*n=49:*	*n=133:*	*0,05*
- meer informatievermijdend	41 (23%)	23 (30%)	18 (17%)		17 (35%)	24 (18%)	
- neutraal	91 (50%)	40 (53%)	51 (48%)		21 (43%)	70 (53%)	
- meer informatiezoekend	50 (27%)	13 (17%)	37 (35%)		11 (22%)	39 (29%)	
Inschatting *BRCA* expertise							
- meerwaarde UMC: kennis	*n=188:* 99 (53%)	*n=78:* 16 (21%)	*n=110:* 83 (75%)	*<0,001 **	*n=50:* 13 (26%)	*n=138:* 86 (62%)	*<0,001 **
- meerwaarde UMC: uitleg	*n=188:* 128 (68%)	*n=78:* 24 (31%)	*n=110:* 104 (95%)	*<0,001 **	*n=49:* 23 (47%)	*n=139:* 105 (76%)	*<0,001 **

* Statistisch significant (p<0,05). TMSI: Threatening Medical Situations Inventory.

met decisional conflict, verwerkingsstrategie en diagnose MC. Het significantie toetsingsniveau was 0,05 (tweezijdig) en data werden geanalyseerd met SPSS 20.0.

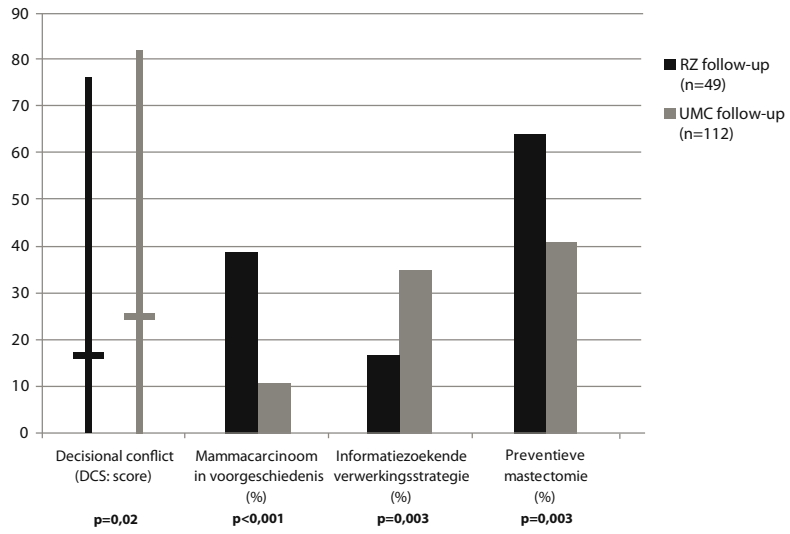
RESULTATEN

BRCA-mutatiedraagsters

De vragenlijst werd ingevuld door 192 van 402 (48%) *BRCA*-mutatiedraagsters (Tabel 1). Responders verschilden niet van non-responders wat betreft *BRCA1* versus *BRCA2*, eerst geteste familielid versus bekende *BRCA*-familie, leeftijd en jaren sinds *BRCA*-uitslag.

Decisional conflict rondom MC preventie

BRCA-mutatiedraagsters in UMC follow-up hadden meer moeite met besluitvorming rondom MC preventie (decisional conflict: p=0,02; Tabel 2, Figuur 2) en meer spijt van hun keuze (p=0,01), waarbij zij minder vaak PM hadden ondergaan dan *BRCA*-mutatiedraagsters in RZ follow-up (p=0,003; Figuur 2). Dit verschil gold voor *BRCA*-mutatiedraagsters zonder MC (p=0,003) maar niet voor *BRCA*-mutatiedraagsters mét MC (p=0,34). *BRCA*-mutatiedraagsters in UMC follow-up waren ook vaker beïnvloed door



Figuur 2: Verschillen tussen *BRCA*-mutatiedraagsters (n=191) op basis van locatie van begeleiding voor mammacarcinoom (MC) preventie: 1) UMC follow-up (n=112, 58%); 2) regionale ziekenhuis (RZ) follow-up (n=80, 42%); wat betreft % preventieve mastectomie uitgevoerd, % mammacarcinoom in voorgeschiedenis, % neiging tot een informatiezoekende verwerkingsstrategie en mediaan [range] van decisional conflict (DCS) score.

Tabel 2: Kenmerken (N (%) of mediaan [range]) van besluitvorming rondom preventie van mammacarcinoom (MC) van *BRCA*-mutatie draagsters (n=192) verdeeld op locatie van begeleiding voor MC preventie: 1) regionale ziekenhuis (RZ) follow-up; 2) UMC follow-up; en verdeeld op wel of geen diagnose mammacarcinoom (MC).

Kenmerk	Totaal (n=192)	Verdeling: locatie MC preventie			Verdeling: diagnose MC		
		RZ (n=80)	UMC (n=112)	p-waarde	Wel MC (n=51)	Geen MC (n=141)	p-waarde
Moeite met besluitvorming (decisional conflict, DCS: 0-100, Cronbach's α=0,92)	*n=182:* 22 [0 – 82]	*n=74:* 18 [0 – 77]	*n=108:* 25 [0 – 82]	*0,02 **	*n=45:* 18 [0 – 77]	*n=137:* 23 [0 – 82]	*0,31*
Preventieve mastectomie (PM)	96 (50%)	51 (64%)	45 (40%)	*0,003 **	28 (55%)	68 (48%)	*0,51*
Tevreden keuze preventie	*n=187:*	*n=74:*	*n=111:*	*0,001 **	*n=47:*	*n=140:*	*0,17*
- sterk mee eens	81 (43%)	44 (58%)	37 (33%)		24 (51%)	57 (41%)	
- mee eens	83 (44%)	26 (34%)	57 (51%)		19 (40%)	64 (46%)	
- niet mee (on)eens	20 (11%)	6 (8%)	14 (13%)		4 (9%)	16 (11%)	
- (sterk) mee oneens	3 (2%)	0 (0%)	3 (3%)		0 (0%)	3 (2%)	
Spijt keuze preventie (decisional regret, DRS: 0-100, α=0,83)	*n=183:* 20 [0 – 80]	*n=75:* 15 [0 – 55]	*n=108:* 25 [0 – 80]	*0,01 **	*n=46:* 15 [0 – 60]	*n=137:* 20 [0 – 80]	*0,37*
Shared decision making	*n=189:*	*n=78:*	*n=111:*	*0,96*	*n=49:*	*n=140:*	*0,13*
- eigen keuze	117 (62%)	48 (62%)	69 (62%)		26 (53%)	91 (65%)	
- gezamenlijke keuze	63 (34%)	27 (35%)	37 (33%)		20 (41%)	44 (31%)	
- vooral advies van arts	8 (4%)	3 (4%)	5 (5%)		3 (6%)	5 (4%)	
Arts van meeste invloed	*n=186:*	*n=77:*	*n=108:*	*<0,001 **	*n=49:*	*n=137:*	*0,001 **
- geen invloed door arts	42 (23%)	15 (20%)	26 (24%)		10 (20%)	32 (23%)	
- arts: RZ	52 (28%)	48 (62%)	4 (4%)		23 (47%)	29 (21%)	
- arts: UMC	92 (49%)	14 (18%)	78 (72%)		16 (33%)	76 (56%)	
Advies van meeste invloed	*n=167:*	*n=65:*	*n=102:*	*0,003 **	*n=39:*	*n=128:*	*0,10*
- geen invloed door arts	42 (25%)	16 (25%)	26 (25%)		10 (26%)	32 (25%)	
- mammasurveillance	46 (28%)	7 (11%)	39 (39%)		6 (15%)	40 (31%)	
- geen specifiek advies	47 (28%)	21 (32%)	26 (25%)		10 (26%)	37 (29%)	
- preventieve mastectomie	32 (19%)	21 (32%)	11 (11%)		13 (33%)	19 (15%)	

* Statistisch significant (p<0,05).

DCS: Decisional Conflict Scale. DRS: Decisional Regret Scale.

advies van UMC specialisten (p<0,001) en advies mammasurveillance (p<0,001). Shared decision making verschilde niet (Tabel 2). Enkelen noemden verwarrende verschillen in voorlichting tussen specialisten: 5% noemde dringend adviseren versus juist afhouden van preventief opereren, 3% noemde verschillen in surveillance of operatief beleid.

Algemene kenmerken

BRCA-mutatiedraagsters in UMC follow-up waren wat betreft verwerkingsstrategie vaker informatiezoekend oftewel hadden meer informatiebehoefte (p=0,003; Tabel 1, Figuur 2) en gaven vaker meerwaarde aan het UMC voor *BRCA*-expertise (kennis p<0,001; uitleg p<0,001) dan *BRCA*-mutatiedraagsters in RZ follow-up. *BRCA*-mutatiedraagsters in RZ follow-up waren vaker gediagnosticeerd met MC dan *BRCA*-mutatiedraagsters in UMC follow-up (p<0,001; Figuur 2).

Voorgeschiedenis MC

BRCA-mutatiedraagsters met MC waren ouder bij *BRCA*-uitslag (p<0,001), vaker laag opgeleid (p=0,001) en gaven minder meerwaarde aan het UMC voor *BRCA*-kennis (p<0,001) en uitleg (p<0,001) dan *BRCA*-mutatiedraagsters zonder MC (Tabel 1).

Keuze OvC preventie

In RZ follow-up hadden meer *BRCA*-mutatiedraagsters de maximale adviesleeftijd bereikt voor RRSO (74% versus 55%, p=0,007) met minder spijt van hun keuze voor OvC preventie (5 [0–60] versus 20 [0–50], p=0,001) dan *BRCA*-mutatiedraagsters in UMC follow-up. Het verschil in RRSO tussen RZ (77%) en UMC follow-up (65%) bleek niet significant (p=0,08). *BRCA*-mutatiedraagsters met MC hadden vaker de maximale adviesleeftijd voor RRSO bereikt (80% versus 56%, p=0,002) en RRSO ondergaan (86% versus 63%, p=0,004) met minder spijt van hun preventiekeuze (5 [0–60] versus 20 [0–50], p=0,02) dan *BRCA*-mutatiedraagsters zonder MC. Bij evaluatie van toekomstige plannen voor deze leeftijdsafhankelijke RRSO hadden bijna alle *BRCA*-mutatiedraagsters de intentie om uiteindelijk RRSO te ondergaan (95%).

Psychologische aspecten

BRCA-mutatiedraagsters rapporteerden gemiddeld weinig psychische problemen (Tabel 3). Follow-up locatie gaf geen verschil. Wel scoorden *BRCA*-mutatiedraagsters met MC anders dan degenen zonder MC (tabel 3): hogere stress (p=0,05) en onzekerheid (p=0,02), lager lichaamsbeeld (p=0,003), meer problemen met seksueel functioneren (p=0,01) en plezier (p=0,02) en hogere risicoperceptie MC na PM (p<0,001).

Tabel 3: Psychologische kenmerken (mediaan [range]) van BRCA-mutatie draagsters (n=192) verdeeld op locatie van begeleiding voor MC preventie: 1) UMC follow-up; 2) regionale ziekenhuis (RZ) follow-up; en verdeeld op wel of geen diagnose mammacarcinoom (MC).

Kenmerk	Totaal (n=192)	Verdeling: locatie MC preventie			Verdeling: diagnose MC		
		RZ (n=80)	UMC (n=112)	p-waarde	Wel MC (n=51)	Geen MC (n=141)	p-waarde
MC-specifieke stress (IES/SVL: 0-75, Cronbach's α=0,94)	6 [0 – 65]	8 [0 – 53]	6 [0 – 65]	*0,25*	11 [0 – 53]	5 [0 – 65]	*0,05 **
Impact van genetisch testen (MICRA)							
- subschaal Stress (0-30, α=0,82)	11 [0 – 30]	11 [0 – 30]	12 [0 – 28]	*0,27*	13 [0 – 26]	11 [0 – 30]	*0,20*
- subschaal Onzekerheid (0-45, α=0,74)	13 [0 – 39]	12 [1 – 30]	13 [0 – 39]	*0,23*	15 [4 – 35]	13 [0 – 39]	*0,02 **
- subschaal Positieve Ervaringen (0-20, α=0,51)	9 [0 – 20]	9 [0 – 15]	10 [0 – 20]	*0,30*	8 [0 – 16]	10 [0 – 20]	*0,50*
Lichaamsbeeld (EORTC-QLQ-BR23 subschaal BRBI: 0-100, α=0,92) **	83 [0 – 100]	75 [0 – 100]	83 [0 – 100]	*0,06*	67 [0 – 100]	83 [0 – 100]	*0,003 **
Seksueel functioneren (EORTC-QLQ-BR23 subschaal BRSEF: 0-100, α=0,95) ***	33 [0 – 100]	33 [0 – 100]	17 [0 – 100]	*0,22*	33 [0 – 100]	17 [0 – 100]	*0,01 **
Seksueel plezier (EORTC-QLQ-BR23 subschaal BRSEE: 0-100) ***	33 [0 – 100]	33 [0 – 100]	33 [0 – 100]	*0,51*	33 [0 – 100]	0 [0 – 100]	*0,02 **
MC risico perceptie (0-100)							
- voor preventieve mastectomie	80 [0 – 100]	80 [5 – 100]	75 [0 – 100]	*0,16*	80 [10 - 100]	80 [0 - 100]	*0,32*
- na preventieve mastectomie	10 [0 – 95]	10 [0 – 85]	5 [0 – 95]	*0,08*	20 [0 – 95]	5 [0 – 80]	*<0,001 **

* Statistisch significant (p<0,05).

** Functioneel: hogere score betekent minder problemen.

*** Symptomatisch: hogere score betekent meer problemen.

IES/SVL: Impact of Event Scale (origineel in Engels) / Schok Verwerking Lijst (Nederlandse vertaling). EORTC-QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Breast Cancer module met 23 vragen. BRBI = BReast Body Image. BRSEF = BReast SExual Functioning. BRSEE = BReast SExual Enjoyment.

Samenwerking *BRCA*-zorg

De helft (52%) van de *BRCA*-mutatiedraagsters had geen mening over de samenwerking tussen regionale ziekenhuizen en het UMC; 8% merkte hier niets van. Als verbeterpunten noemde 9% onderlinge communicatie, 7% overeenstemming van beleid, 5% meer *BRCA*-kennis in de regio en 4% meer *BRCA*-zorg naar de regio.

Multivariate analyse

Zowel decisional conflict (OR 0.97 [0.95–0.99]) als meer informatiezoekende verwerkingsstrategie (OR 0.26 [0.10–0.73]) en diagnose MC (OR 6.99 [3.03–16.15]) leverden onafhankelijke bijdragen aan RZ follow-up.

Regionale oncologische specialisten

Van de 105 regionale oncologische specialisten respondeerden er 47 (45%): onder medisch oncologen was er 42% respons, chirurgen 29% en gynaecologen 68%.

Rol van het UMC

Van de responders was 32% tevreden over overleg met het UMC expertiseteam en 21% had verbeterpunten (sneller overleg, geen overname van zorg); 47% had geen ervaring met dergelijk overleg. De meerderheid (70%) gaf voorkeur aan een eenmalig UMC consult voor patiënten om gevolgen voor familieleden (89%) en preventieadviezen (83%) te bespreken. Vooral passieve ondersteuningsmiddelen bijv. website (66%) of zakkaartjes met verwijscriteria (60%) werden gewaardeerd.

Preventieadviezen

Voor mammasurveillance (Tabel 4) adviseerde 12% van internisten en chirurgen conform de landelijke richtlijn, 31% gaf geen eigen advies maar volgde het UMC expertiseteam en 54% gaf een advies dat afweek (soort controles, leeftijden, frequentie) van de richtlijn. Bij diagnose MC adviseerde 26% bilaterale mastectomie, bij *BRCA*-mutatiedraagsters zonder MC adviseerde 11% PM. Voor OvC preventie adviseerde 81% van gynaecologen alleen RRSO, 19% adviseerde daarnaast gynaecologische surveillance voorafgaand aan RRSO.

Tabel 4: Advisering mamma/ovariumcarcinoom preventie (N(%)) van oncologische specialisten uit regionale ziekenhuizen (n=47) voor *BRCA*-mutatiedraagsters.

Kenmerk	Totaal (n=47)	Internisten (n=14: 30%)	Chirurgen (n=12: 25%)	Gynaecologen (n=21: 45%)
Advies voor schema mammacarcinoom (MC) surveillance				
- advies geheel conform landelijke IKNL richtlijn	3 (7%)	0 (0%)	3 (25%)	0 (0%)
- volgt advies expertiseteam	11 (23%)	6 (43%)	2 (17%)	3 (14%)
- laat advies rondom MC preventie over aan andere specialist	9 (19%)	1 (7%)	0 (0%)	8 (38%)
- afwijkende leeftijd of frequentie	11 (23%)	5 (36%)	4 (33%)	2 (10%)
- afwijkende soort controles	13 (28%)	2 (14%)	3 (25%)	8 (38%)
Advies bij *BRCA*-mutatiedraagster met recent MC				
- mammasparend	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- unilaterale mastectomie	2 (4%)	1 (7%)	1 (8%)	0 (0%)
- bilaterale mastectomie	12 (26%)	4 (36%)	3 (25%)	4 (19%)
- geen specifiek advies of alle opties	33 (70%)	8 (57%)	8 (67%)	17 (81%)
Advies gezonde *BRCA*-mutatiedraagster rondom MC preventie				
- mammasurveillance	2 (4%)	1 (7%)	1 (8%)	0 (0%)
- preventieve mastectomie (PM)	5 (11%)	1 (7%)	2 (17%)	2 (10%)
- geen specifiek advies of beide opties	40 (85%)	12 (86%)	9 (75%)	19 (91%)
Advies gezonde *BRCA*-mutatiedraagster rondom ovariumcarcinoom (OvC) preventie				
- jaarlijkse OvC surveillance	2 (4%)	2 (14%)	0 (0%)	0 (0%)
- preventieve bilaterale salpingoöphorectomie (RRSO)	26 (55%)	4 (29%)	5 (42%)	17 (81%)
- geen specifiek advies of beide opties	19 (41%)	8 (57%)	7 (58%)	4 (19%)

BESCHOUWING

Er blijken verschillen tussen *BRCA*-mutatiedraagsters die begeleid worden in regionale ziekenhuizen of het UMC. *BRCA*-mutatiedraagsters in de regio waren vaker gediagnosticeerd met MC; *BRCA*-mutatiedraagsters in UMC follow-up hadden meer decisional conflict en/of informatiebehoefte rondom MC preventie en/of waren vaker presymptomatisch. Hierbij kozen zij minder vaak voor preventieve mastectomie. Dit suggereert dat deze vrouwen een specifieke subgroep onder *BRCA*-mutatiedraagsters betreft met meer behoefte aan academische begeleiding.

In ander onderzoek kozen *BRCA*-mutatiedraagsters met MC driemaal vaker PM dan degenen zonder MC[67], maar in onze studie was dit niet verschillend. Er is geen eerdere

vergelijking gemaakt tussen UMC en regionale ziekenhuizen, maar in onze groep *BRCA*-mutatiedraagsters kozen juist vrouwen zonder MC vaker voor PM in de regio dan in het UMC. Dit lijkt vooral te maken hebben met het verschil in decisional conflict. Een preventieve operatie is onomkeerbaar: vrouwen in decisional conflict zullen een ingreep vaker uitstellen en ter overbrugging kiezen voor mammasurveillance.[60] Dit kan te maken hebben met verwerkingsstrategie: meer decisional conflict speelde reeds onder jong volwassenen getest voor *BRCA*-mutaties met behoefte aan veel informatie.[156] Mogelijk zien zij vaker zowel voor- als nadelen, leidend tot decisional conflict; andersom kan decisional conflict leiden tot zoeken naar meer informatie om hiermee dit conflict op te heffen.

UMC's en regionale ziekenhuizen vervullen verschillende behoeften van patiënten en hebben ieder een eigen functie binnen de *BRCA*-zorg: de regionale ziekenhuizen begeleiden vooral vrouwen die reeds bekend zijn met een diagnose MC, terwijl UMC's begeleiding bieden aan vrouwen die presymptomatisch zijn, of meer twijfel of informatiebehoefte hebben. Dit komt overeen met de wens van de regionale specialisten: de meerderheid wenst een eenmalig adviesgesprek tussen *BRCA*-mutatiedraagsters en het UMC expertiseteam om gevolgen voor de patiënt en haar familieleden (veelal presymptomatisch) en preventieadviezen te bespreken. Regionale samenwerking is heel belangrijk om te zorgen dat de individuele *BRCA*-mutatiedraagster op de juiste plaats optimale zorg krijgt, waarbij aandacht besteed wordt aan eenduidige advisering over surveillance volgens de landelijke richtlijnen.

Een sterk punt van dit onderzoek is het gebruik van gevalideerde vragenlijsten. De retrospectieve opzet is echter gevoelig voor recall bias (zaken anders herinneren dan de werkelijkheid) en cognitieve dissonantie (onbewust herzien van meningen om ze meer in overeenstemming met elkaar te brengen en daarmee spanning te reduceren).[182] Voor *BRCA*-mutatiedraagsters is het lastig om verschillende adviezen te rapporteren: 40-80% van informatie in een medisch consult wordt direct vergeten.[121] Mogelijk is de respons onder *BRCA*-mutatiedraagsters laag (48%) vanwege het versturen van de vragenlijsten vlak na een landelijke vragenlijst studie in dezelfde patiëntengroep (HEBON: landelijke onderzoeksgroep naar erfelijke borst- en eierstokkanker). De groep regionale specialisten is klein en beperkt tot de ziekenhuizen in samenwerking met het Radboudumc.

Conclusie

Regionale ziekenhuizen en UMC's hebben ieder een eigen rol binnen de *BRCA*-zorg. *BRCA*-mutatiedraagsters in beide types ziekenhuizen verschilden van elkaar: vrouwen met MC gaan meestal (terug) naar de regio, terwijl vrouwen onder UMC begeleiding meer decisional conflict en/of informatiebehoefte hebben en/of presymptomatisch

zijn. Regionale specialisten hebben voorkeur voor eenmalige UMC adviesgesprekken voor patiënten om gevolgen voor familieleden en preventieadviezen te bespreken. Regionale samenwerking is heel belangrijk om te zorgen dat de individuele *BRCA*-mutatiedraagster op de juiste plaats de optimale zorg krijgt.

BELANGENCONFLICT EN FINANCIËLE ONDERSTEUNING

Geen.

LEERPUNTEN

Wat is bekend?

- Vaststelling van een *BRCA*-mutatie vindt plaats bij afdelingen Genetica van universitair medisch centra (UMC's), waarbij klinisch genetische spreekuren zowel in regionale ziekenhuizen als in UMC's gehouden worden.
- *BRCA*-mutatiedraagsters kunnen voor follow-up (intensieve surveillance of preventieve operaties) begeleid worden door het multidisciplinair UMC expertiseteam of door specialisten in de eigen regio, met of zonder een eenmalig consult bij het UMC expertiseteam.
- Keuzes van *BRCA*-mutatiedraagsters ten aanzien van kanker preventie worden mede bepaald door patiëntkenmerken: mogelijk verschillen *BRCA*-mutatiedraagsters die begeleid worden in een UMC van degenen die begeleid worden in een regionaal ziekenhuis.

Wat is nieuw?

- *BRCA*-mutatiedraagsters reeds gediagnosticeerd met mammacarcinoom gingen voor verdere begeleiding vaker (terug) naar een regionaal ziekenhuis, terwijl vrouwen onder specialistische UMC begeleiding meer decisional conflict en/of meer informatiebehoefte hadden en/of presymptomatisch waren.
- De helft van de regionaal werkende oncologisch specialisten had nog geen ervaring met overleg met het UMC expertiseteam; de meerderheid gaf voorkeur aan eenmalige UMC adviesgesprekken voor de *BRCA*-mutatiedraagsters met aandacht voor familieleden en preventieadviezen.
- Regionale ziekenhuizen en UMC's vervullen verschillende patiëntbehoeften en hebben hiermee ieder een eigen functie binnen de *BRCA*-zorg: regionale samenwerking is heel belangrijk om te zorgen dat de individuele *BRCA*-mutatiedraagster op de juiste plaats de optimale zorg krijgt.

Chapter 9

General discussion

"We keep moving forward, opening new doors and doing new things, because we're curious and curiosity keeps leading us down new paths."

(Walt Disney)

GENERAL DISCUSSION

Primary prevention is heralded as the most effective way to fight cancer: between one third and half of all cancers could be prevented based on our current knowledge of risk factors.[195] Despite these expected benefits, primary prevention remains insufficiently integrated into clinical practice and more attention is called to modifiable cancer risk factors include smoking, alcohol, diet, physical activity.[195] Beyond these common risk factors, a minority of people is at highly increased lifetime risk for certain cancers, based on a variety of genetic predispositions.[21] These patients can take preventive actions such as early surveillance or prophylactic surgery to effectively lower their risks of cancer incidence and mortality.[9,10] Therefore genetics also provide excellent opportunities for this highly sought-after primary prevention.[195] But these preventive actions are only possible if patients are, in fact, aware of carrying these risk factors and if they know which actions are appropriate in their individual situation.

As described in the General Introduction (**Chapter 1**), the cancer genetic diagnostic process can be split into three stages with each their own research needs. Previous literature has shown that hereditary cancer syndromes remain under-recognized[37,38] (**Stage I: Recognition & Referral**) while technical possibilities[2] as well as societal demands[5,196] for genetic testing are ever growing (**Stage II: Genetic Testing & Counseling**), but appropriate guidance and follow-up of hereditary cancer are not always clear[197,198] (**Stage III: Follow-up & Prevention**). To improve patient awareness of hereditary cancer and proper prevention, changes may be necessary in all three stages to aid the integration of primary prevention based on genetic factors into oncologic care. New models of genetic services are currently being developed and evaluated throughout the world, challenging the long-standing tradition of two-visit face-to-face models.[5]

The implementation of health care innovations is often met with certain apprehension. Donald Berwick stated in 2003[7]: "In health care, innovation is hard, but dissemination is even harder." Perceptions of each innovation predict the majority of the rate of spread: what people *think* of the innovation will determine whether or not they will *adopt* this change. Important perceptions include:

1. *benefits versus risks:* how does it help them compared to the known status quo?
2. *compatibility with individual values and needs:* does it fit within their current context?
3. *complexity:* how hard is it to implement? (i.e. the simpler, the better)
4. *trialability:* is there a way to test it on a small scale first? (i.e. pilot testing)
5. *observability:* how easy is it to observe others who try the innovation first?

Changes spread faster when these five perceptions are beneficial. These perceptions are related: for example, reduction of uncertainty in weighing benefits versus risks is made easier if the individual can observe benefits experienced by early adopters in a pilot test prior to full-scale implementation. Therefore it is important to evaluate these early adopter experiences and make them known to the greater majority, for these to follow in their footsteps.[7] Previous chapters have described several studies that evaluated real-life experiences with innovations within the cancer genetic diagnostic process, to inform perceptions held by the larger majority (including other health care professionals) in order to support acceptance and implementation into common clinical practice. This chapter will summarize the principal findings for each stage within the cancer genetic diagnostic process and discuss both their clinical implications and future prospects.

Stage I: Recognition & Referral

> Improved recognition of hereditary cancer can be achieved by two main strategies: improving genetic testing selection criteria and improving access to cancer genetic services (**Chapters 2 through 5**).
> Providing scientific evidence e.g. cost-effectiveness analyses to support changes in selection criteria for genetic testing is useful to encourage further clinical implementation (**Chapter 2**).
> New genetic service models are necessary and often acceptable, especially to affected patients where psychological distress is based on the experience of their cancer diagnosis, not the additional genetic diagnostic procedure (**Chapters 3, 4 and 5**).

Despite growing public awareness of genetic aspects to cancer[5,196], two of the most common forms of hereditary cancer, Lynch syndrome for colorectal and endometrial

cancer (CRC and EC) and *BRCA*-mutations for breast and ovarian cancer (BC and OC)[21] remain under-recognized even today.[37,38] Not identifying families at high risk for cancer prohibits these individuals from taking actions to lower their cancer incidence and mortality[9,10]: these are missed chances for primary cancer prevention.

Several strategies are possible to improve detection of hereditary cancer. On one hand, selection criteria for referral to genetic diagnostics should be continuously refined, such as the age limit for CRC tumor genetic testing recently being raised from 50 to 70 years.[24,29,75] **Chapter 2** showed that this novel strategy was indeed cost-effective and would lead to a fourfold detection of Lynch syndrome compared to current practice. Refinement of selection criteria can therefore have great benefits. Furthermore, providing scientific evidence on clinical efficacy and cost-effectiveness may support the implementation of these guideline changes among various stakeholders, including policy makers.[199]

However, literature showed there to be insufficient knowledge of familial cancer risk assessment amongst non-genetic professionals[37]: efforts to provide improved selection criteria are for naught when not put into practice by clinicians selecting patients. Education of clinicians alone does not improve the referral rate of high risk patients[40]: therefore, easy-to-use online referral tests based on national guidelines[36,57] were made available at **www.radboudumc.nl/hereditarycancer.**[200] These tests guide appropriate family history collection, based on the consideration "the simpler, the better"[7]: clinicians no longer need to consult complex criteria manually but receive an automatic recommendation for referral to clinical genetics, early surveillance or neither. Non-medical staff used the referral test for correct advice in 84% of patient cases[200] while physicians without the test achieved only 65%.[37] This has led to widespread use in daily practice by general practitioners and oncology practices and may augment further genetic training of clinicians.[201]

Another strategy is to improve patient access to clinical genetic services for further counseling and germline testing, especially considering growing public awareness and demands[196], leading to the development of new models of service delivery.[5] One such novel procedure was described in **Chapter 3 through 5** for *BRCA*-mutation testing in BC patients, replacing the pre-test intake consultation by an informational package sent to patients' homes and only providing post-test face-to-face counseling. This allowed BC patients who preferred these alternative information formats and/or felt burdened by additional hospital visits to initiate genetic testing close to home. Similar new models are being evaluated elsewhere, including the use of pre-visit tailored websites[157], the choice after an intake consultation to learn test results by letter instead of face-to-face

counseling[147] and certain risk groups being offered *BRCA*-testing by pre-test telephone contact, with post-test counseling only following a positive *BRCA*-result (otherwise reported by letter[158]). All these studies showed high satisfaction without long-term distress: if psychological distress is present, this seems to be based primarily on the experience of cancer rather than the additional genetic diagnostic procedure (**Chapters 4-5**). This demonstrates that patients are well able to withstand these necessary changes in cancer genetic services models.[5]

However, a further attitude shift among the greater majority of genetic professionals towards "P5 medicine"[202,203] is necessary: *p*redictive, *p*ersonalized, *p*reventive, *p*articipatory and *p*sychocognitive. We would argue that this also involves prioritizing the individual needs and preferences of patients over the traditional model of personal pre- and post-test genetic counseling. Trepanier e.a.[5] previously identified perception of reduced quality of cancer genetics services as one of the main barriers to using non-traditional models, especially post-test counseling (85%). But high patient satisfaction and low distress were reported in aforementioned studies where pre-test information is provided by alternative (not face-to-face) means, seeming to suggest that no such quality reduction occurs from the perspective of the central stakeholder: the patients.

Such attitude shifts have happened successfully before: adjusting the Huntington-based model of two to only one pre-test consultation in cancer genetics, following reassuring patient experiences and expected increases in test requests.[8] But there seems to be some resistance to further shifts now, despite recognition of the need for more accessible genetic services.[5] It is interesting to note that genetic counseling is based on a long standing foundation of non-directiveness and shared decision making when it comes to the decision *whether* to undergo genetic testing.[204] But when attempts are made to hold the same ethical standards to the decision *how* to undergo genetic testing, these are met with far more hesitation. Instead, this basis of preserving patient autonomy should be ripe for more personalization of cancer genetic services, inviting more patient participation as called for in modern medicine.[4] Future studies should evaluate more possible service models that are aimed at individual preferences for information, exploring different avenues for fulfilling the need for and shift towards P5 medicine in cancer genetics[202] whilst upholding the quality of genetic counseling.[5]

Stage II: Genetic Testing & Counseling

> Standardized psychosocial support by social workers or psychologists for generalized patient groups is excessive: such support is more effective if focused on specific subgroups in need (**Chapter 6**).

> Offering new genetic technologies in a clinical diagnostic setting is acceptable if accompanied by proper genetic counseling and informed consent procedures which are open to changes based on further experiences (**Chapter 7**).

Being faced with the possibility of increased risks for cancer can have a psychosocial impact, even without clinically relevant distress.[13] Attempts to evaluate these intricate psychodynamics within genetic counseling have long been made[3] but only in recent years have these aspects been summarized into six main psychosocial issues: coping with cancer risk, practical issues, family-related problems, children-related problems, living with cancer and emotional reactions.[13] While standard genetic counseling is sufficient for the majority of patients, a quarter of patients experiences serious psychological distress[13]: certain patients are known to be at higher risk of such distress.[18] Additional decisional support is made mandatory for certain risk groups prior to the start of genetic testing: for example, young adults between 18 and 25 years who may learn of their genetic status years before surveillance starts.[46] However, **Chapter 6** showed that the great majority of these young adults did not regret their decision to be tested and such generalized support is excessive. But there was a subgroup of young adults who experienced decisional conflict: rather than spreading out these precious resources across an entire group, psychosocial support would be most effective if focused on those in need. Recently developed screening questionnaires may be useful in helping clinical geneticists and genetic counselors identify those specific patients.[205]

At the same time, the focus of psychosocial support could also shift from the pre-test to the post-test setting following identification of mutation carriers. Among cancer patients, adolescent and young adult patients already diagnosed with cancer between the ages of 15 and 39 are increasingly recognized as a unique group requiring special services. The Radboudumc has developed an adolescent and young adult (AYA) expertise center to provide this particular subgroup with integrated medical-technical and psychosocial care.[206] But unaffected young adults at genetic risk for cancer may still feel out of place in these systems, not having experienced an actual cancer diagnosis themselves.[207] This "previvor" experience i.e. having a hereditary predisposition for cancer but not yet having had the disease[208] can be generalized to all age groups, but young adults deal with additional concerns in their development as independent adults (e.g. moving out, new careers, starting a family).[46,47,66,172,207,209] In future studies, the expertise of both oncologic specialists caring for young adult cancer patient/survivors as well as genetic counselors providing guidance to families at high risk for cancer should be joined together in a new type of young adult previvor services. Not only would this address this age group's unique set of support needs and preferences, but it would also help to cross bridges

between genetics and medical oncology, aiding in the integration of primary cancer prevention.

Another situation where psychological distress could occur, are uncertain[54] or unexpected results.[210] The increasing availability of genome-wide technologies[2] also leads to the increasing possibility of such results leading to many discussions about the acceptability of integrating these technologies into clinical diagnostic settings.[53] However, looking at certain precedents, this is a natural progression of advancing genetic technologies with chromosomal microarray leading the way.[211] A similar trend of initial hesitation was seen in these technologies which could more precisely identify chromosomal abnormalities, resulting in a significantly higher diagnostic yield compared to traditional karyotyping but still seen as "experimental" at first.[212] Nowadays, chromosomal microarrays are recommended as first-line diagnostic test in patients with developmental delay, intellectual disability, autism spectrum disorders and multiple congenital anomalies.[213] The majority of abnormal microarray results have had clinical consequences, which were expected to help further improve patients' medical management and health.[214]

Similarly, two-step exome sequencing was shown to outperform traditional single-gene sequencing in a diagnostic setting.[56] Additional to this clinical utility, **Chapter 7** described a study of patient experiences with gene panels based on exome sequencing (step 1) in clinical diagnostics, with high acceptance and low distress. Although evaluation following full exome-wide analyses (step 2) is yet to follow, the current study results provide an optimistic expectation of exome-wide results being received well by patients. Other recent studies regarding clinical implementation of NGS showed a variety in patient preferences to receive unsolicited findings[215] but emphasize the wish for an opt-out for (certain) unsolicited findings.[162,215,216] Various models have already been suggested but not yet evaluated in practice.[162] Unsolicited findings can be categorized into: 1) life-saving/immediate clinical utility, 2) potential/moderate clinical utility, 3) reproductive significance and 4) personal/recreational significance.[217] A qualified disclosure policy was proposed where the first category was standard and mandatory, whereas the other three categories could be opted into by patients as additional packages.[217] This approach could strike the right balance between patient autonomy and physician duty to report, thus may be the future of NGS informed consent procedures. These various studies show that new genetic technologies are acceptable if accompanied by proper genetic counseling and informed consent procedures, which are open to adjustments based on new experiences in practice.

Considering these positive past and current experiences, taking sequencing to the next level of whole-genome[2] seems both achievable and acceptable. But beyond ethical

and psychosocial concerns, there is currently an inflexible divide between research and clinical care limiting both.[218] Aggregation of large-scale sequencing data is necessary to provide conclusive results in either setting and this data is best used pooled together for shared use. Although there are concerns such as the therapeutic misconception (patients' mistaken belief that research will benefit them directly), this may help many more patients and families to end otherwise long diagnostic odysseys.[218] Future studies are needed to identify effective strategies for bridging this gap between research and clinical care, which are carefully balanced not to add therapeutic misconceptions[218] or problems with financial coverage as previously seen with the clinical implementation of chromosomal microarray technologies.[213]

Stage III: Follow-up & Prevention

> Regional and university hospitals fulfill different patient needs in the clinical follow-up of *BRCA*-mutation carriers for cancer prevention: regional collaboration is essential to ensure that the individual *BRCA*-mutation carrier receives optimal care at the appropriate location (**Chapter 8**).

The main benefit of identifying individuals with a hereditary cancer syndrome, is the ability to take preventive action and lower cancer incidence and mortality[9,10] especially in unaffected carriers. *BRCA*-mutations and Lynch syndrome (LS) are the two most well-known forms of hereditary cancer[21] but only explain a small proportion (estimated 5-10%) of all cancer cases[195] therefore non-genetic professionals are not likely to come across a great number of these patients. Specific knowledge of these hereditary cancer syndromes is important to support these patients, for which continued medical education in cancer genetics was shown to be vital.[72] In our study described in **Chapter 8**, *BRCA*-mutation carriers previously diagnosed with BC were more likely to go or return to regional hospitals. Conversely, those women who chose to be supported in a university hospital had higher decisional conflict and/or information need and/or were more likely presymptomatic.

This shows that patient characteristics differ between the two follow-up locations: regional and university hospitals therefore fulfill different patient needs in clinical follow-up of *BRCA*-mutation carriers. Care for those patients who do not experience high decisional conflict and/or information need and/or already have a cancer history, could shift more towards regional hospitals i.e. second line of health care. Care for those patients expressing a need for specialized support (e.g. decisional conflict) should remain in university hospitals (third line) with special expertise in hereditary cancer.

Regional collaboration between these hospitals is therefore essential to ensure that the individual *BRCA*-mutation carrier receives optimal care at the appropriate location.

Therefore, while all *BRCA*-mutation carriers should be provided with consistent cancer prevention information in all lines of health care, they should not be considered a uniform group for "one size fits all" policies. These patients have individual preferences not just for the type of health care received, but also the location thereof. Especially with increased public awareness[196] and the gradual shift of clinical genetic services towards regional hospitals[192], university hospitals with specific hereditary cancer expertise should thus focus on continued medical education of regional specialists[72] and providing more support tools not just for referral[201] but also for clinical follow-up once a hereditary predisposition has been identified. This ensures quality *BRCA*-care across all lines of health care, allowing patients their free choice of preferred and most appropriate follow-up location.

Methodological Reflections

Strengths

The Radboudumc is a frontrunner when it comes to innovative genetic health care, such as being among the first to implement two-step exome sequencing in a clinical diagnostic setting.[56] The studies described in this thesis are unique as they took advantage of being in the midst of this fast-developing field and first-in-line institution, using these opportunities to help develop and evaluate such innovations in this real life setting. This provided more realistic outcomes than previous discussions and studies found in literature based on hypothetical or research settings, or based on the views of professionals rather than patients as the central stakeholders.[51,183,219-227]

Resulting from the previous lack of practical experience, clinical recommendations and policies were often based on such expert opinions and assumptions. However, these may not always reflect reality. For example, another recent study demonstrated discordant perspectives of different stakeholders on reporting unsolicited findings: while clinicians focused on the clinical relevance as the determining factor for whether or not to report, the lay groups emphasized autonomy and patients' right to choose which results to receive, accepting consequences of possible anxiety or uncertainty.[228] The purpose of the studies described in this thesis was to evaluate realistic settings directly to test these clinician assumptions and create a scientific basis for further policy-making, either through patient experiences or models based on real-life data.

When patient experiences regarding subjects within this thesis had previously been studied, these studies were often qualitative of nature.[46,47,66,172,207,209,215,228] This was suited for exploring certain recurrent themes for informing further research. This thesis focused on the use of quantitative measures, to allow more precise measurement of change over time (**Chapters 3-5 and 7**), testing for differences between groups (**Chapters 3-6 and 8**) or to determine specific subgroups to focus support on (**Chapters 6 and 8**). Neither research methodologies is superior or inferior to the other; rather the quantitative studies described in this thesis were often based on and then considered complements to the previous qualitative studies found, both shedding further light on these research subjects from different angles.

Limitations

The studies described in this thesis have several limitations in common. Some studies of patient experiences were retrospective (**Chapters 6 and 8**) and therefore sensitive to recall bias and cognitive dissonance. Furthermore, although correlations were found, it was not always possible to measure prospectively to determine the direction of causal relations: one example is the correlation between decisional conflict and monitoring coping style, which were suggested in both **Chapters 6 and 8**. Assessing these measures in prospective studies may further elucidate the precise relation between the two psychological aspects in the context of genetic testing.

Other limitations of some studies were non-randomization (**Chapters 3-5**) or being able only to evaluate acceptors of a certain genetic procedure (**Chapters 6 and 7**), which limited generalizability of these study results. Regarding the non-randomization of DNA-direct, this was a conscious choice as the main study outcome was patient preference for the novel DNA-direct procedure instead of the traditional DNA-intake procedure: without any interest among patients, the effort of implementing such a new procedure would be for naught. Regarding the evaluation of only acceptors, this was limited by the ethical allowances of our research studies as we were restricted from approaching those who had declined genetic testing, although it would also be valuable to know their motivations for this choice.

Finally, some studies were limited by small study samples, for example due to restriction in lab capacity (**Chapter 7**), although significant results were found even with these limited numbers.

Implications for Clinical Practice

The main goal of cancer genetic services is to identify those individuals at increased risk for cancer. Current literature suggests that we are still missing many families at risk.[37,38]

New strategies discussed in this thesis were proven to be effective: the next step is to implement these strategies into clinical practice.

First, the detection of hereditary cancers is highly dependent on the criteria used to identify these syndromes. Basic hallmarks of hereditary cancer are young age and positive family history, but exact referral criteria are subject to change depending on new insights. However, this may also broaden the group of eligible patients, accompanied by higher costs: clinicians and financial stakeholders may therefore be hesitant to implement these changes unless these costs are proven to be balanced by greater benefits. Cost-effectiveness analyses such as described in **Chapter 2** are necessary to provide this scientific evidence to reduce uncertainty regarding the economical consequences and thereby support the clinical implementation of these changes[7] i.e. all patients diagnosed with CRC at age 70 or younger should undergo tumor genetic testing for Lynch syndrome.

Another aspect to consider is patient access to cancer genetic services. Considering higher demands for these services and an increased call for patient participation in health care, other models beyond the traditional two-visit format should be explored.[5] Our study on the novel DNA-direct procedure described in **Chapters 3-5** adds to the ever-growing body of literature[147,157,158] showing that patients find these new models of cancer genetic services acceptable, despite concerns about the lower priority on face-to-face counseling. Models involving post-test genetic counseling may increase patient access to genetic testing, as pre-test information could be provided in alternative and possibly preferred formats. Patients could even arrange genetic testing without additional hospital visits, which is especially important as genetic tests are often concentrated within expert but geographically sparse clinical genetic centers. Detecting hereditary cancer is only possible if patients are given the opportunity to make use of these tests: clinicians should explore new models bringing these tests and these patients closer together, while upholding the high quality of genetic counseling. The DNA-direct procedure evaluated here is one such model considered acceptable for clinical practice.

Similarly, additional psychosocial support prior to genetic testing may be necessary in certain patients, but current practice made such support mandatory as a "one size fits all" approach to a generalized group of patients. One such group consists of young adults between 18 and 25 years as described in **Chapter 6**. Instead such support should focus only on those patients portraying specific vulnerability or decisional conflict regarding their choice whether or not to start genetic testing. Social workers and psychologists are a sparse resource in cancer genetic service centers: this allows them to be more effective. Clinical geneticists and genetic counselors should explore certain aspects correlating

to decisional conflict – such as coping style and the presence of family mutations – to identify those specific patients in need of decisional support and personalized information as a filter step prior to referral for additional psychosocial support. Counselors may also consider using standard screening questionnaires[205] as a tool to help them select these patients.

The road towards genetic testing is undergoing aforementioned changes, but innovative genetic technologies such as next generation sequencing are also breaking into clinical diagnostics.[2] Current evaluations of early patient experiences with two-step exome sequencing described in **Chapter 7** show that genetic professionals should not hesitate to offer this technology in clinical diagnostic settings, provided it is framed within proper genetic counseling and informed consent procedures. Further experiences with these novel techniques are necessary to increase its clinical benefits: fine-tuning the existing gene panels, expansion to other heterogenic diseases, as well as allowing for more personalized informed consent with patient opt-out possibilities. Continued evaluation of worldwide experiences with NGS, be it on a whole exome or even genome level, must also continue to inform such genetic testing and counseling policies, especially as more becomes known about the nature and frequency of the much-discussed unsolicited (or incidental) findings.[162]

Finally, once a hereditary cancer syndrome has been identified, patients are usually recommended long-term clinical follow-up. Though university hospitals are often expertise centers for hereditary cancer syndromes, patients may prefer regional hospitals for the location of their follow-up consultations as shown in *BRCA*-mutation carriers (**Chapter 8**) especially in the case of a previous cancer diagnosis. Patients in decisional conflict about their cancer prevention management options may be more likely to opt for that specialized support within university hospitals. This underlines a specific focus for academic expertise centers: patients with decisional conflict and/or higher information need.

Future Prospects

We live in the so-called Information Age: the Internet serves as an easily accessible worldwide network with increasing capabilities for information storage and spread.[229] This goes hand in hand with the health care wide call for shared decision-making[4]: in a 2014 eHealth monitor by Nictiz and NIVEL, 65% of Dutch health care users reported having looked online for health information in the past year, of whom 39% used this to decide whether or not to consult a doctor.[230] eHealth services are increasingly important to patient self-care, and such patient engagement in their own health care may lead to better health care outcomes.[231]

Our online referral tests which guide clinicians in familial cancer risk assessment[201] may therefore also be suitable for direct use by patients and the general public. In fact, when these referral tests were initially made available as self-tests to the general public for a short period of time, 256 users filled in an online questionnaire in which the majority of 71% reported the self-test provided them with more certainty and/or reassurance regarding their familial risk of hereditary cancer: only 3% was less reassured by the self-test.[200] Results from the DNA-direct procedure (**Chapters 3-5**) also suggest that patients are capable of handling such genetic information with less face-to-face time. The self-test could potentially act as a filter for questions regarding hereditary cancer: only those with a moderate or high risk are advised to go to their general practitioner, while the majority at low risk is reassured. However, there are concerns about triggering adverse psychological effects among unsuspecting healthy individuals and the self-test was therefore modified into a professional-aimed referral test. Studies are currently ongoing to evaluate the effect of these self-tests on participants in cancer population screening programs, as a step towards renewed public availability of the self-tests.

However, as pointed out earlier, genetic factors only explain a minority of all cancers.[195] There is also a wide range of lifestyle risk factors which can be influenced by patients themselves, such as smoking, diet and physical activity. Better awareness of these factors may lead to more patient empowerment through better-informed self-care.[231] This may be especially important in those already at high risk through genetic predispositions, as literature consistently suggests that especially smoking and a high body mass index further increases CRC risk in Lynch syndrome patients.[232] Further studies will be performed to assess the knowledge of lifestyle factors among Lynch syndrome patients and evaluate the effects of information about these lifestyle factors on both knowledge and behavior.

Final Considerations

These are exciting times for cancer genetics, as many different evolutions are ongoing simultaneously. This includes (but is not limited to) "P5" health care for integration of predictive, personalized, preventive, participatory and psychocognitive aspects[202,203]; more patient empowerment and shared decision making[4], higher demands for genetic services leading to the need to develop and evaluate new service delivery models[5] and novel technologies showing higher diagnostic yield in different patient groups.[2]. All the more reason to bring all these different developments together into a joint culmination of more transparent and multidisciplinary cooperation in the development of future health care innovations, taking into account the necessary perceptions for successful clinical implementation.[7] To do this, we must let go of our professional (or otherwise)

assumptions and follow our scientific instincts to test these hypotheses instead: only then can we prove or disprove the acceptability of these innovations.

Finally, Albert Einstein stated many decades ago: "Intellectuals solve problems, geniuses prevent them." In other words: our priority in oncologic care should not only be curing cancer, but preventing cancer from ever happening as well!

Chapter 10

Summary/samenvatting

"Don't fear failure so much that you refuse to try new things. The saddest summary of a life contains three descriptions: could have, might have, and should have."

(Louis E. Boone)

SUMMARY

Approximately 5 to 10% of all cancers are based on a hereditary predisposition. The process of identifying these families with hereditary cancer can be split into three stages:

Stage I) Recognition & Referral
Stage II) Genetic Testing & Counseling
Stage III) Follow-up & Prevention

Considering increased demands for cancer genetic services, this three-stage process has become subject to a variety of innovations. Some were borne from technical advancements, whereas others were meant to achieve more patient-centered health care. **Chapter 1** describes each stage within the cancer genetic diagnostic process and provides background for specific subjects of attention with associated research needs. These needs are addressed by the studies further described in this thesis.

Hereditary cancer syndromes such as Lynch syndrome (LS) or *BRCA*-mutations remain under-recognized. To improve detection of LS, experts had recommended raising the age limit for tumor genetic testing in colorectal cancer (CRC) patients from diagnosis at age 50 years or below (current practice) to age 70 years or below (experimental strategy). This recommendation was based on expert opinion alone, therefore **Chapter 2** provides scientific evidence that this novel strategy is indeed cost-effective and results in fourfold increased detection of LS patients (i.e. LS mutation carriers). Implementation is important to find family relatives of those LS patients currently missed and to offer them life-saving surveillance. A new version of the Dutch national guideline "Hereditary colorectal cancer" is currently being developed to include the new age limit of 70 years. This novel strategy greatly simplifies the process of LS identification: half of all CRC cases

is diagnosed at 70 years or below and can therefore be immediately tested prior to clinical genetic referral based on a single criterion.

To identify *BRCA*-mutations, currently no tumor genetic test exists. Therefore an alternative pathway to improve detection of these families must be found. The face-to-face consultation has long been the golden standard, but is not the most effective method of providing information: 40% to 80% of verbal medical information is immediately forgotten by patients. Therefore **Chapters 3-5** describe a novel procedure for breast cancer (BC) genetic diagnostics, where BC patients referred for genetic counseling could choose to replace the face-to-face intake consultation (DNA-intake) with telephone, written and digital information sent to patients' homes (DNA-direct). More patients indeed opted for DNA-direct over DNA-intake to read pre-test information in the comfort of their own home without an additional hospital visit. Moving the first face-to-face contact to only post-test also allowed the genetic counselor to immediately discuss personal consequences of *BRCA*-results for patients and their families. Less consultation time was lost covering basic information about BC and heredity, allowing more space for psychosocial aspects. Patients were highly satisfied and reported no increased distress on either short or long term.

Testing for adult-onset genetic cancer susceptibility such as LS or *BRCA*-mutations is generally not performed on minors below 18 years of age. But concerns have also been expressed about testing those from age 18 years, but still younger than the surveillance age of 25 years. This could leave a considerable time gap between learning of their hereditary predisposition and being able to act upon this knowledge. However, **Chapter 6** demonstrates that almost none of these young adults reported regret of their choice to test between 18 and 25 years. Standardized psychosocial support for all young adults is time-consuming especially with a growing number of patients seeking out cancer genetic services. Our quantitative analysis revealed that some young adults who experienced decisional conflict, especially those leaning towards a monitoring coping style or with paternal inheritance, and may be the appropriate target group for such support. This study did not introduce a new element to cancer genetic diagnostics, but instead removed the mandatory "one size fits all" pre-test consultation with a social worker or psychologist. This support can be more effective when focused on individual patients in need of such support, identified by genetic counselors.

A major technological advancement in genetics is so-called next generation sequencing (NGS) such as whole exome sequencing, allowing the exons of all genes to be sequenced simultaneously rather than conventional single-gene testing. Although these technologies show great promise, ethical concerns about possible unsolicited

or unclear findings led to hesitation to offer these novel techniques in clinical diagnostics. The Radboudumc was among the first to implement exome sequencing in a clinical diagnostic setting. **Chapter 7** describes early patient experiences, showing high satisfaction and no increased distress following results of targeted gene panel analysis, comparable to conventional single-gene testing. Our study was the very first to quantify experiences of a larger group of patients using standardized and validated psychological questionnaires. These study results, combined with higher diagnostic yield proven in other studies, supported local expansion of eligible diseases and a change in informed consent procedure. This change allowed patients to opt out of exome-wide analysis, limiting to targeted gene panels to avoid higher probabilities of unsolicited or unclear findings.

The last phase within the cancer genetic diagnostic process concerns follow-up and prevention. Once a *BRCA*-mutation has been identified, these mutation carriers can choose to be supported for follow-up care in a regional or university hospital. **Chapter 8** evaluates differences between these two groups of *BRCA*-mutation carriers. *BRCA*-mutation carriers previously diagnosed with BC were more likely to go or return to regional hospitals, whereas women supported by UMCs had higher decisional conflict and/or information need and/or were more likely presymptomatic. This matched regional specialists' preference for a one-time consultation between the UMC expert team and *BRCA*-mutation carriers to discuss consequences for the patient and her family relatives (usually presymptomatic) and cancer prevention recommendations. This led to the conclusion that both regional and university hospitals fulfill different patient needs in the follow-up of *BRCA*-mutation carriers. Regional collaboration is therefore essential to ensure that the individual *BRCA*-mutation carrier receives optimal care at the appropriate location.

Finally, **Chapter 9** summarizes the principal findings of the aforementioned studies, as well as the clinical implications and future prospects following from these findings. Many ongoing evolutions – "P5" health care, shared decision making, new genetic service delivery models, novel genetic technologies – should be brought together into a joint culmination of more transparent and multidisciplinary cooperation in the development of health care innovations concerning hereditary cancer. Professionals should take care not to assume, but to test their suspicions as scientific hypotheses. Oncologic care should focus not only on curing those already struck by illness, but also primary prevention as the most effective way to fight cancer.

SAMENVATTING

Ongeveer 5 tot 10% van alle kanker gevallen wordt veroorzaakt door een erfelijke aanleg. De procedure om deze families met erfelijke kanker te herkennen kan worden opgesplitst in drie fasen:

Fase I) Herkenning & Verwijzing
Fase II) Genetisch Testen & Counseling
Fase III) Follow-up & Preventie

De vraag naar kanker genetische zorg neemt toe, waardoor deze drie-fase procedure onderhevig is aan verschillende innovaties. Sommigen komen voort uit technische vooruitgangen, terwijl anderen bedoeld zijn om meer patiëntgerichte zorg te bereiken. **Hoofdstuk 1** omschrijft elke fase van de kanker genetische diagnostische procedure en geeft de achtergrond weer voor specifieke aandachtspunten met de bijbehorende onderzoek behoeften. Deze behoeften vormen de basis voor de wetenschappelijke studies die vervolgens in dit proefschrift worden omschreven.

Erfelijke kanker syndromen zoals Lynch syndroom (LS) of *BRCA*-mutaties worden nog steeds niet voldoende herkend. Om de herkenning van LS te verbeteren, hadden experts aanbevolen om de leeftijdsgrens voor tumor genetisch testen in patiënten met colorectaal carcinoom (CRC) van een maximale diagnoseleeftijd 50 jaar (huidige praktijk) te verhogen naar een maximale diagnoseleeftijd van 70 jaar (experimentele strategie). Deze aanbeveling was alleen gebaseerd op de opinie van experts. Daarom verschaft **Hoofdstuk 2** wetenschappelijk bewijs dat deze nieuwe strategie inderdaad kosteneffectief is en leidt tot de diagnose LS bij viermaal zoveel patiënten. Implementatie is belangrijk omdat de familieleden van de patiënten met LS die nu nog worden

gemist, daarmee kunnen profiteren van preventie of vroegdiagnostiek van een CRC. Een nieuwe versie van de Nederlandse richtlijn "Erfelijke darmkanker" wordt momenteel ontwikkeld, inclusief deze nieuwe leeftijdsgrens van 70 jaar. Deze nieuwe strategie zal het diagnostisch proces bij LS versimpelen, omdat patiënten met een colorectaal carcinoom tot en met 70 jaar meteen worden getest op basis van dit enkele criterium voorafgaand aan verwijzing door een klinisch geneticus.

Momenteel bestaat er geen tumor genetische test om *BRCA*-mutaties te identificeren. Om herkenning van deze families te verbeteren, moet daarom gezocht worden naar een alternatief. Het persoonlijke (face-to-face) consult is al lange tijd de gouden standaard, maar blijkt niet de meest effectieve vorm van informatievoorziening: 40% tot 80% van verbale medische informatie wordt direct door patiënten vergeten. Daarom beschrijven **Hoofdstukken 3-5** een nieuwe procedure voor borstkanker (BK) genetische diagnostiek, waarbij patiënten met BK die verwezen worden voor genetische counseling, de keuze krijgen om het face-to-face intake gesprek (DNA-intake) te vervangen met telefonisch, schriftelijke en online informatie om thuis te ontvangen (DNA-direct). Meer patiënten kozen inderdaad DNA-direct in plaats van DNA-intake om pre-test informatie op eigen gemak thuis door te nemen zonder een extra ziekenhuisbezoek. Door het eerste face-to-face contact alleen post-test te laten plaatsvinden, kon de genetisch counselor ook direct de persoonlijke gevolgen van de *BRCA*-uitslag voor de patiënt en haar familie bespreken. Minder consult tijd ging verloren aan de uitleg van algemene informatie over BK en erfelijkheid, zodat meer ruimte overbleef voor psychosociale aspecten. Patiënten waren zeer tevreden en rapporteerden geen verhoging van distress op korte of lange termijn.

Het testen van erfelijke aanleg voor kanker wat zich uit op volwassen leeftijd, zoals LS of *BRCA*-mutaties, wordt over het algemeen niet gedaan bij minderjarigen jonger dan 18 jaar. Echter zijn er ook zorgen over het testen van personen vanaf 18 jaar, die nog jonger zijn dan de surveillance leeftijd van 25 jaar. Mogelijk betekent dit een aanzienlijk tijdsgat tussen het weten dat zij een erfelijke aanleg hebben en de mogelijkheid om op deze kennis actie te ondernemen. Echter, **Hoofdstuk 6** laat zien dat bijna geen van deze jongvolwassenen spijt hebben van hun keuze om zich te laten testen tussen 18 en 25 jaar. Standaard psychosociale ondersteuning voor alle jongvolwassenen is tijdrovend, vooral gezien het groeiend aantal patiënten voor kanker genetische zorg. Onze kwantitatieve analyse liet zien dat sommige jongvolwassenen wel moeite met besluitvorming (decisional conflict) ervoeren, vooral degenen met een actieve informatiezoekende verwerkingsstijl of paternale overerving. Dit vormt mogelijk de juiste doelgroep voor dergelijke ondersteuning. Deze studie betrof niet het introduceren van een nieuw onderdeel in kanker genetische diagnostiek, maar nam juist het verplichte "one size fits

all" pre-test consult met een maatschappelijk werker of psycholoog weg. Deze ondersteuning is meer effectief als deze gericht is op individuele patiënten met behoefte aan deze begeleiding, herkend door de genetische counselors.

Een enorme technische vooruitgang binnen de genetica is het zogenaamde next generation sequencing (NGS) zoals exoom sequencing, waarmee de exonen van alle genen tegelijkertijd bekeken worden in tegenstelling tot traditioneel enkel-gen testen. Hoewel deze technieken veelbelovend zijn, leiden ethische zorgen rondom ongevraagde of onduidelijke bevindingen tot terughoudendheid bij het aanbieden van deze nieuwe technieken in klinische diagnostiek. Het Radboudumc was een van de eerste centra die exoom sequencing implementeerde in een klinisch diagnostische setting. **Hoofdstuk 7** omschrijft de eerste patiëntervaringen, met hoge tevredenheid en geen verhoogde distress na de uitslagen van gerichte genenpanels, vergelijkbaar met traditionele enkelgen testen. Onze studie was de allereerste die deze ervaringen van een grote groep patiënten kwantificeerde, gebruikmakend van gestandaardiseerde en gevalideerde psychologische vragenlijsten. Deze studieresultaten, tesamen met de hogere diagnostische opbrengst aangetoond in andere studies, leidden tot lokale uitbreiding van ziekten die in aanmerking komen voor exoom sequencing en een verandering van het informed consent beleid. Door deze verandering kunnen patiënten kiezen om geen exoom-brede analyse uit te voeren (opt-out), om zich te beperken tot gerichte genenpanels en hogere kansen op ongevraagde of onduidelijke bevindingen te vermijden.

De laatste fase binnen de kanker genetische diagnostische procedure betreft follow-up en preventie. Als een *BRCA*-mutatie eenmaal is ontdekt, kunnen deze mutatiedraagsters kiezen voor follow-up begeleiding in een regionaal ziekenhuis of een universitair medisch centrum (UMC). **Hoofdstuk 8** evalueert verschillen tussen deze twee groepen van *BRCA*-mutatiedraagsters. *BRCA*-mutatiedraagsters gediagnosticeerd met borstkanker gingen vaker (terug) naar de eigen regio, terwijl vrouwen begeleid in een UMC vaker hoger decisional conflict (oftewel moeite met besluitvorming rondom borstkanker preventie) en/of meer informatiebehoefte hadden, en/of vaker presymptomatisch waren. Dit kwam overeen met de voorkeur van regionale specialisten voor een eenmalig consult tussen het UMC expertiseteam en *BRCA*-mutatiedraagsters, om gevolgen voor de patiënt en haar familieleden (veelal presymptomatisch) en kanker preventiemaatregelen te bespreken. Dit leidde tot de conclusie dat regionale ziekenhuizen en UMC's ieder verschillende patiëntbehoeften vervullen bij de follow-up van *BRCA*-mutatiedraagsters. Regionale samenwerking is daarom van uiterst belang om te zorgen dat de individuele *BRCA*-mutatiedraagster de juiste zorg krijgt op de juiste plaats.

Tot slot geeft **Hoofdstuk 9** een samenvatting van de hoofdbevindingen van de voorgenoemde studies, als ook de klinische implicaties en toekomstperspectieven ten gevolge van deze bevindingen. Vele voortgaande evoluties – "P5" gezondheidszorg, gedeelde besluitvorming, nieuwe modellen voor genetische dienstverlening, nieuwe genetische technieken – zouden bijeen gebracht moeten worden tot een gezamenlijk hoogtepunt van meer transparante en multidisciplinaire samenwerking in de ontwikkeling van zorginnovaties rondom erfelijke kanker. Professionals moeten uitkijken voor het maken van aannames, maar hun verdenkingen juist toetsen als zijnde wetenschappelijke hypothesen. Oncologische zorg moet zich richten niet alleen op het beter maken van reeds zieke personen, maar ook primaire preventie als de meest effectieve manier om kanker te bestrijden.

Dankwoord

List of publications

PhD portfolio

Curriculum vitae

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Lieve Guy: hoewel het academische wereldje jou niet ligt, kick je wel op tradities. En op zo'n speciale dag als deze, denk ik ook: wat moet ik toch zonder mijn grote broer? Dat jij mijn paranimf wilde zijn om deze mijlpaal met mij te delen, betekent dan ook enorm veel voor mij. Dank je wel voor al je lieve steun, broertjuh.

My dearest Ross: where to begin? A good part of this PhD project was all about breaking out of my comfort zone, and you were the one giving me the confidence to fly that high, with a safe haven to come home to. Thanks to your neverending love and support, I can follow my own path with you always by my side. I cannot imagine my life – either before or after this PhD – without you. Thank you for putting up with me throughout these years, both at my best and at my worst. I love you with all my heart.

LIST OF PUBLICATIONS

Diagnostiek Lynch-syndroom bij colorectaal carcinoom: Testen van patiënten tot en met 70 jaar is kosteneffectief. *Sie AS*, Mensenkamp AR, Adang EM, Ligtenberg MJL, Hoogerbrugge N. Ned Tijdschr Geneeskd. 2014;158:A8449.

Easy-to-Use Decision Aids for Improved Cancer Family History Collection and Use Among Oncology Practices. *Sie AS*, Brunner HG, Hoogerbrugge N. J Clin Oncol. 2014;32(29):3343.

Fourfold increased detection of Lynch syndrome by raising age limit for tumour genetic testing from 50 to 70 years is cost-effective. *Sie AS*, Mensenkamp AR, Adang EM, Ligtenberg MJL, Hoogerbrugge N. Ann Oncol. 2014;25(10):2001-7.

Patient experiences with gene panels based on exome sequencing in clinical diagnostics: high acceptance and low distress. *Sie AS*, Prins JB, van Zelst-Stams WAG, Veltman JA, Feenstra I, Hoogerbrugge N. Clin Genet. 2015;87(4):319-26.

More breast cancer patients prefer *BRCA*-mutation testing without prior face-to-face genetic counseling. *Sie AS*, van Zelst-Stams WAG, Spruijt L, Mensenkamp AR, Ligtenberg MJL, Brunner HG, Prins JB, Hoogerbrugge N. Fam Cancer. 2014;13(2):143-51.

Can we test for hereditary cancer at 18 years when we start surveillance at 25? Patient reported outcomes. *Sie AS*, Prins JB, Spruijt L, Kets CM, Hoogerbrugge N. Fam Cancer. 2013;12(4):675-82.

DNA-testing for *BRCA1/2* prior to genetic counselling in patients with breast cancer: design of an intervention study, DNA-direct. *Sie AS*, Spruijt L, van Zelst-Stams WAG, Mensenkamp AR, Ligtenberg MJL, Brunner HG, Prins JB, Hoogerbrugge N. BMC Womens Health. 2012;12:12.

PHD PORTFOLIO

Name PhD student: A.S. Sie
Department: Human Genetics
Graduate School: Radboudumc Institute for Health Sciences

PhD period: 01-02-2011 – 31-01-2015
Promotor(s): Prof. dr. N. Hoogerbrugge
Prof. dr. J.B. Prins

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
Radboud Universiteit: Presenteren van uw eigen onderzoek	2012	1.75
PAO Heyendael: Basiscursus klinisch onderzoekers (BROK)	2013	1.75
Clinical PhD council: How to write a medical scientific paper	2011	0.2
b) Seminars & lectures^		
Theme meeting Radboudumc: Exome sequencing	2011	0.1
Radboud Postdoc Initiative: Lunch seminar Time Management for Young Researchers	2011	0.2
Research Institute for Oncology: Theme Meetings	2012	0.1
Sep 2012, Dec 2012, Mar 2013, Apr 2013, May 2013, June 2013, Oct 2013	2012 - 2013	0.7
Workshop on Statistics and Meta-analysis	2012	0.1
Radboud Postdoc Initiative: Lunch seminar (Social) Media Use in Research and Patient Care	2013	0.1
Workshop Thesis Design	2013	0.1
c) Symposia & congresses^		
NCEBP (RIHS) Symposium Nijmegen 2011, 2013	2011 - 2013	0.5
ESHG: European Human Genetics Conference Amsterdam 2011, Nuernberg 2012 #, Paris 2013 #, Milan 2014 #	2011 - 2014	5.5
CaRe Symposium: eHealth: More care or more worry?	2011	0.25
Kwaliteitsmiddag Stafconvent: Social Media in de zorg: een vruchtbare combinatie?	2012	0.1
Vereniging Klinische Genetica Nederland: LOG meeting Utrecht 2011, Rotterdam 2011, Amsterdam 2012, Utrecht 2013	2011 - 2013	1.0
NVHG: Najaarssymposium #	2012	0.75
Werkgroep Klinische Oncogenetica *	2013	0.5
Apps4Health congres #	2013	0.5
IPOS Satellite Symposium	2013	0.1
Research Institute for Oncology: Science Day Berg en Dal 2012 #, 2013 #, 2014 #	2012 - 2014	1.5
HEBON Congres dag Utrecht 2013 *, 2014 *	2013 - 2014	1.0
Mobile Healthcare congres	2013	0.25
Joint UK-Dutch Clinical Genetics Societies Conference # #	2014	1.25
Nederlandse Vereniging voor Psychosociale Oncologie congres *	2014	0.5
7th European Multidisciplinary Colorectal Cancer Congress * #	2014	1.25
Co-creatie eHealth boek bijeenkomst	2014	0.1

d) Other	***e.g.***	
Human Genetics: Literature Discussion series ***	2011 - 2015	3.0
Clinical Oncogenetics: Literature Discussion series ***	2011 - 2015	3.0
Committee Chairperson: MijnZorgnet Community Manager "Erfelijke kanker voor zorgverleners"	2012	1.0
Co-organizer symposium "Up-to-date in erfelijke kanker 2013"	2013	2.0
eHealth Support Committee (journal club) **	2014 - 2015	1.0
TEACHING ACTIVITIES		
e) Lecturing: None		
f) Supervision of internships / other: None		
TOTAL		30.15

* Oral presentation, # Poster presentation

CURRICULUM VITAE

Aisha (officially spelled Ai Sha) Sie was born on the Summer Solstice – June 21st – of the year 1984 in Purmerend, the Netherlands. The daughter of an internist, becoming a physician had been a childhood dream until she became equally fascinated with technology during high school. Following her graduation from the Jan van Egmond College in Purmerend in 2002, she moved to Enschede to study Biomedical Engineering at the University of Twente in an attempt to combine both passions. However, she was quickly drawn more to the "Biomedical" part of her studies.

In 2004, she switched to medical school at the University of Groningen (Rijksuniversiteit Groningen). In her final year of earning her Medical Degree, she did a research internship at the Department of Gynecology and Obstetrics in the University Medical Center Groningen (UMCG) evaluating the decision-making process of ovarian cancer prevention in *BRCA*-mutation carriers. Armed with this novel experience in hereditary cancer research, she started the year of 2011 as a freshly graduated physician researcher at the Department of Human Genetics at the Radboud University Medical Center (Radboudumc) in Nijmegen. This eventually led to the body of work you are currently reading. She will continue working at the Radboudumc as a postdoctoral physician researcher, hoping to further innovate cancer genetic health care – bridging the gap between novel technologies and clinical patient care, after all.

She happily shares a registered partnership with Ross Tuck.

Google Scholar

http://scholar.google.nl/citations?user=xMAINNEAAAAJ

LinkedIn

http://nl.linkedin.com/in/aishasie

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